Splitting the follow-up
C&H 6

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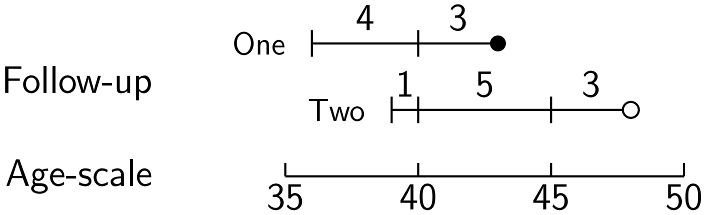
PhD-course in Epidemiology,
Department of Biostatistics,
Wednesday 15 May 2013

Stratification by age

If follow-up is rather short, age at entry is OK for age-stratification.

If follow-up is long, use stratification by categories of **current age**, both for:
No. of events, D, and Risk time, Y.



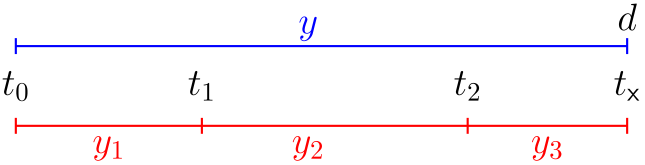
Representation of follow-up data

In a cohort study we have records of:
Events and **Risk time**.

Follow-up data for each individual must have (at least) three variables:

- Date of entry — `entry` — date variable.
- Date of exit — `exit` — date variable
- Status at exit — `fail` — indicator-variable (0/1)

Specific for each *type* of outcome.



Probability

$\mathrm{P}(d \text{ at } t_\mathsf{x} | \text{entry } t_0)$

$= \mathrm{P}(\text{surv } t_0 \rightarrow t_1 | \text{entry } t_0)$

$\times \mathrm{P}(\text{surv } t_1 \rightarrow t_2 | \text{entry } t_1)$

$\times \mathrm{P}(d \text{ at } t_\mathsf{x} | \text{entry } t_2)$

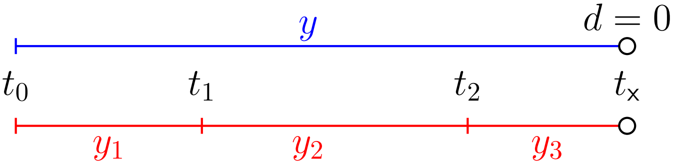
log-Likelihood

$d \log(\lambda) - \lambda y$

$= 0 \log(\lambda) - \lambda y_1$

$+ 0 \log(\lambda) - \lambda y_2$

$+ d \log(\lambda) - \lambda y_3$



Probability

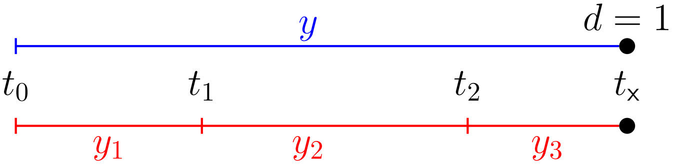
$$\mathrm{P}(\text{surv } t_0 \rightarrow t_\mathsf{x} | \text{entry } t_0)$$

$$= \mathrm{P}(\text{surv } t_0 \rightarrow t_1 | \text{entry } t_0)$$
$$\times \mathrm{P}(\text{surv } t_1 \rightarrow t_2 | \text{entry } t_1)$$
$$\times \mathrm{P}(\text{surv } t_2 \rightarrow t_\mathsf{x} | \text{entry } t_2)$$

log-Likelihood

$$0 \log(\lambda) - \lambda y$$

$$= 0 \log(\lambda) - \lambda y_1$$
$$+ 0 \log(\lambda) - \lambda y_2$$
$$+ 0 \log(\lambda) - \lambda y_3$$



Probability	log-Likelihood
$\mathrm{P}(\text{event at } t_x \mid \text{entry } t_0)$	$1\log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_0 \rightarrow t_1 \mid \text{entry } t_0)$	$= 0\log(\lambda) - \lambda y_1$
$\times \mathrm{P}(\text{surv } t_1 \rightarrow t_2 \mid \text{entry } t_1)$	$+ 0\log(\lambda) - \lambda y_2$
$\times \mathrm{P}(\text{event at } t_x \mid \text{entry } t_2)$	$+ 1\log(\lambda) - \lambda y_3$

Aim of dividing time into bands:

- Compute rates in different bands of:
  - age
  - calendar time
  - disease duration
  - ...
- Allow rates to vary along the timescale:

$$\begin{aligned} & 0\log(\lambda) - \lambda y_1 \\ +\, & 0\log(\lambda) - \lambda y_2 \\ +\, & d\log(\lambda) - \lambda y_3 \end{aligned} \quad \rightarrow \quad \begin{aligned} & 0\log(\lambda_1) - \lambda_1 y_1 \\ +\, & 0\log(\lambda_2) - \lambda_2 y_2 \\ +\, & d\log(\lambda_3) - \lambda_3 y_3 \end{aligned}$$

Prerequisites of splitting time

Origin: The date where the time scale is 0:

- Age — 0 at date of birth
- Disease duration — 0 at date of diagnosis
- Occupation exposure — 0 at date of hire

Intervals: How should it be subdivided:

- 1-year classes? 5-year classes?
- Equal length — not necessarily.

Cohort with 3 persons:

Id	Bdate	Entry	Exit	St
1	14/07/52	04/08/65	27/06/97	1
2	01/04/54	08/09/72	23/05/95	0
3	10/06/87	23/12/91	24/07/98	1

- Define strata: 10-years intervals of current age.
- Split Y for every subject accordingly
- Treat each segment as a separate unit of observation.
- Keep track of exit status in each interval.

Splitting the follow up

	subj. 1	subj. 2	subj. 3
Age at **E**ntry:	13.06	18.44	4.54
Age at e**X**it:	44.95	41.14	11.12
Status at exit:	Dead	Alive	Dead
Y	31.89	22.70	6.58
D	1	0	1

Where did the pieces go?

	subj. 1		subj. 2		subj. 3		$\sum$	
Age	Y	D	Y	D	Y	D	Y	D
0–	0.00	0	0.00	0	5.46	0	5.46	0
10–	6.94	0	1.56	0	1.12	1	8.62	1
20–	10.00	0	10.00	0	0.00	0	20.00	0
30–	10.00	0	10.00	0	0.00	0	20.00	0
40–	4.95	1	1.14	0	0.00	0	6.09	1
$\sum$	31.89	1	22.70	0	6.58	1	60.17	2

Time-splitting with SAS: %Lexis

```
%Lexis( data=a, entry=Entry, exit=Exit, fail=St,
        origin=bdate, scale=365.25, cuts=0 to 80 by 10 ) ;

id       Bdate       Entry        Exit   St     risk left

 1  14/07/1952  03/08/1965  14/07/1972   0   6.9432   10
 1  14/07/1952  14/07/1972  14/07/1982   0  10.0000   20
 1  14/07/1952  14/07/1982  14/07/1992   0  10.0000   30
 1  14/07/1952  14/07/1992  27/06/1997   1   4.9528   40
 2  01/04/1954  08/09/1972  01/04/1974   0   1.5606   10
 2  01/04/1954  01/04/1974  31/03/1984   0  10.0000   20
 2  01/04/1954  31/03/1984  01/04/1994   0  10.0000   30
 2  01/04/1954  01/04/1994  23/05/1995   0   1.1417   40
 3  10/06/1987  23/12/1991  09/06/1997   0   5.4634    0
 3  10/06/1987  09/06/1997  24/07/1998   1   1.1211   10
```

Time-splitting with Stata `stset, stsplit`

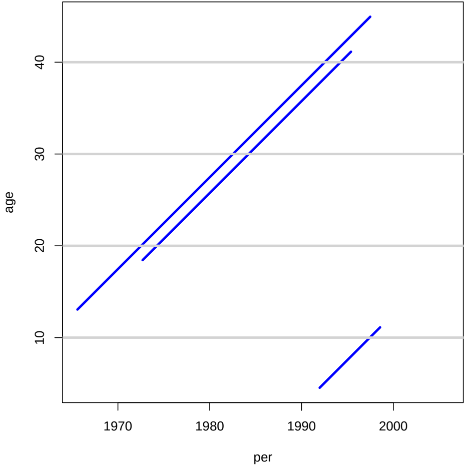
```
stset  Exit,  failure(St==1)  entry(Entry)  origin(Bdate) /*
          */  scale(365.25) id(Id)

stsplit cAge, at(40(10)70) after(Bdate)

gen py = _t - _t0

table cAge, c(sum _d sum py) format(%9.2f)
```

Time-splitting with R `Lexis`, `splitLexis`

```
library( Epi )

Lx <- Lexis( entry = list( per = Entry,
                           age = Entry-Bdate ),
              exit = list( per = Exit ),
       exit.status = factor( St, labels=c("Alive","Dead") ),
              data = coh )

Ls <- splitLexis( Lx, breaks=seq(0,100,10), time.scale="age" )

lex.id      per    age lex.dur lex.Cst lex.Xst Id    Bdate     En
     1 1965.589 13.056   6.943   Alive   Alive  1 1952.533 1965.
     1 1972.533 20.000  10.000   Alive   Alive  1 1952.533 1965.
     1 1982.533 30.000  10.000   Alive   Alive  1 1952.533 1965.
     1 1992.533 40.000   4.952   Alive    Dead  1 1952.533 1965.
     2 1972.686 18.439   1.560   Alive   Alive  2 1954.246 1972.
     2 1974.246 20.000  10.000   Alive   Alive  2 1954.246 1972.
     2 1984.246 30.000  10.000   Alive   Alive  2 1954.246 1972.
     2 1994.246 40.000   1.141   Alive   Alive  2 1954.246 1972.
     3 1991.974  4.536   5.463   Alive   Alive  3 1987.437 1991.
     3 1997.437 10.000   1.121   Alive    Dead  3 1987.437 1991.
```

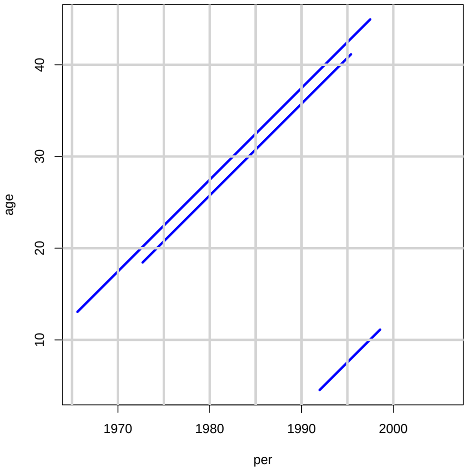
Time-splitting with R `Lexis`, `splitLexis`

```
plot( Ls, col="blue", lwd=3 )
```



Time-splitting with R `Lexis`, `splitLexis`

```
Ls <- splitLexis( Ls, breaks=seq(1900,2000,5), time.scale="per"
plot( Ls, col="blue", lwd=3 )
```



What happens when splitting time?

- **From:** one record per person
- **To:** many records per person,
- — each representing a short piece of follow-up time.
- **Same** total no. events
- **Same** total follow-up time (PYs)
- Possibility of different rates in different intervals.

What about the Cox-model?

Data for Cox-regression has only one record per person.

- It allows rates to vary over time (the baseline)
- — internally in the program, the data is split
- Time-dependent covariates require multiple records per person
- Additional time-scales require multiple records per person

What happens when splitting time?

We are actually mimicking a **continuous** surveillance of the study population.

For each little piece of follow up we attach the relevant covariates:

- Fixed covariates. (sex, genotype, ...)
- Deterministically time-varying covariates: age, time since entry, calendar time — all derived from the current date.
- Non-deterministically varying covariates. (current smoking habits, occupational exposure, ...)

Models for time-split data

For follow-up data we make linear models for:

$$\eta = \log(\lambda Y) = \log(\lambda) + \log(Y)$$

by telling the software that D is Poisson.

If the model for the rate λ is multiplicative:

$$\log(\lambda) = x_1\beta_1 + x_2\beta_2 + \cdots + \log(Y)$$

Among the covariates are some that model the time-effect (in the IHD-example, age).

Independent observations?

When we split data, each individual contributes several observations, which are not independent.

Yet, we treat them as such.

The likelihood contribution from one person is a **product** of **conditional** probabilities.

Because the likelihood is a product, we can use the program (`proc genmod`, `glm`, `...`) as if they were independent; we are only interested in getting the maximum likelihood estimates.

The offset

Need to take account of the "covariate" $\log(Y)$, which has a regression coefficient fixed to be one:

$$\log(\lambda Y) = x_1\beta_1 + x_2\beta_2 + \cdots + \log(Y)$$

$\log(Y)$ is called an **offset**-variable.

Analysis of results from `%Lexis`

- D — events in the variable `fail`.
- Y — risk time = difference: `exit - entry`. Enters in the model via $\log(Y)$ as offset.
- Covariates are:
  - timescales (age, calendar time, time since entry)
  - other variables for this person (constant or *assumed* constant in each interval).
- Model rates using the covariates in `proc genmod`
- Note: there is no difference in how time-scales and other covariates are treated in the model.

Poisson model for split data

- Each interval contribute λY to the log-likelihood.
- All intervals with the same set of covariate values (age,exposure,...) have the same λ.
- The log-likelihood contribution from these is $\lambda \sum Y$ — the same as from aggregated data.
- The event intervals contribute each $D \log \lambda$.
- The log-likelihood contribution from those with the same lambda is $\sum D \log \lambda$ — the same as from aggregated data.
- The log-likelihood is the same for split data and aggregated data — no need to tabulate first.