

# Epidemiology for PhD students

**Bendix Carstensen** Steno Diabetes Center Copenhagen  
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<http://BendixCarstensen.com/EpiPhD/F2019>

Department of Biostatistics, University of Copenhagen, Spring 2019

From /home/bendix/teach/Epi/KU-epi/slides/slides.tex

Monday 6<sup>th</sup> April, 2019, 16:46

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## Splitting the follow-up

Tuesday 9 April 2019

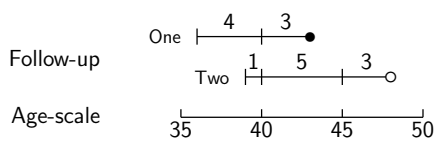
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rec-split

## 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,  $Y$ .
- ▶ —  $(D, Y)$  is the fundamental observation in follow-up studies.



Splitting the follow-up (rec-split)

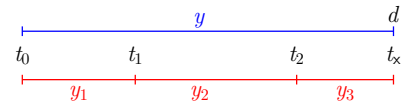
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## Representation of follow-up data

- ▶ In a cohort study we have records of (**Events, 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.

Splitting the follow-up (rec-split)

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Probability

$$\begin{aligned} &P(d \text{ at } t_x | \text{entry } t_0) \\ &= P(\text{surv } t_0 \rightarrow t_1 | \text{entry } t_0) \\ &\times P(\text{surv } t_1 \rightarrow t_2 | \text{entry } t_1) \\ &\times P(d \text{ at } t_x | \text{entry } t_2) \end{aligned}$$

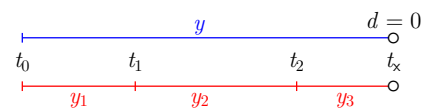
log-Likelihood

$$\begin{aligned} &d \log(\lambda) - \lambda y \\ &= 0 \log(\lambda) - \lambda y_1 \\ &+ 0 \log(\lambda) - \lambda y_2 \\ &+ d \log(\lambda) - \lambda y_3 \end{aligned}$$

... assuming that the rate  $\lambda$  is constant

Splitting the follow-up (rec-split)

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Probability

$$\begin{aligned} &P(\text{surv } t_0 \rightarrow t_x | \text{entry } t_0) \\ &= P(\text{surv } t_0 \rightarrow t_1 | \text{entry } t_0) \\ &\times P(\text{surv } t_1 \rightarrow t_2 | \text{entry } t_1) \\ &\times P(\text{surv } t_2 \rightarrow t_x | \text{entry } t_2) \end{aligned}$$

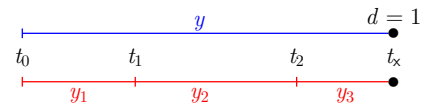
log-Likelihood

$$\begin{aligned} &0 \log(\lambda) - \lambda y \\ &= 0 \log(\lambda) - \lambda y_1 \\ &+ 0 \log(\lambda) - \lambda y_2 \\ &+ 0 \log(\lambda) - \lambda y_3 \end{aligned}$$

... assuming that the rate  $\lambda$  is constant

Splitting the follow-up (rec-split)

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Probability

$$\begin{aligned} &P(\text{event at } t_x | \text{entry } t_0) \\ &= P(\text{surv } t_0 \rightarrow t_1 | \text{entry } t_0) \\ &\times P(\text{surv } t_1 \rightarrow t_2 | \text{entry } t_1) \\ &\times P(\text{event at } t_x | \text{entry } t_2) \end{aligned}$$

log-Likelihood

$$\begin{aligned} &1 \log(\lambda) - \lambda y \\ &= 0 \log(\lambda) - \lambda y_1 \\ &+ 0 \log(\lambda) - \lambda y_2 \\ &+ 1 \log(\lambda) - \lambda y_3 \end{aligned}$$

... assuming that the rate  $\lambda$  is constant

Splitting the follow-up (rec-split)

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## Aim of dividing time into bands:

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

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

Splitting the follow-up (rec-split)

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## 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
- ▶ Time scale is always **time since** some origin.

**Intervals:** How should the scale be subdivided:

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

## Time-splitting with SAS: %Lexis

```
%Lexis( data=a, entry=Entry, exit=Exit, fail=St,
        origin=bdate, scale=365.25, breaks=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

## 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	10

- ▶ 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, *D*, in each interval.

## Time-splitting with Stata stset, stsplitt

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

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

gen py = _t - _t0

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

## Splitting the follow up

	subj. 1	subj. 2	subj. 3
Age at Entry:	13.06	18.44	4.54
Age at eXit:	44.95	41.14	11.12
Status at exit:	Dead	Alive	Dead
<i>Y</i>	31.89	22.70	6.58
<i>D</i>	1	0	1

## 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" )
```

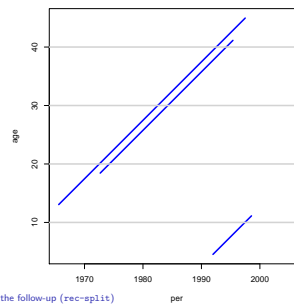
lex.id	per	age	lex.dur	lex.Cst	lex.Xst	Id	Bdate	Entry	Exit	St
1	1965.589	13.056	6.943	Alive	Alive	1	1952.533	1965.589	1997.485	1
1	1972.533	20.000	10.000	Alive	Alive	1	1952.533	1965.589	1997.485	1
1	1982.533	30.000	10.000	Alive	Alive	1	1952.533	1965.589	1997.485	1
1	1992.533	40.000	4.952	Alive	Dead	1	1952.533	1965.589	1997.485	1
2	1972.686	18.439	1.560	Alive	Alive	2	1954.246	1972.686	1995.388	0
2	1974.246	20.000	10.000	Alive	Alive	2	1954.246	1972.686	1995.388	0
2	1984.246	30.000	10.000	Alive	Alive	2	1954.246	1972.686	1995.388	0
2	1994.246	40.000	1.141	Alive	Alive	2	1954.246	1972.686	1995.388	0
3	1991.974	4.536	5.463	Alive	Alive	3	1987.437	1991.974	1998.559	1
3	1997.437	10.000	1.121	Alive	Dead	3	1987.437	1991.974	1998.559	1

## Where did the pieces go?

Age	subj. 1		subj. 2		subj. 3		$\Sigma$	
	<i>Y</i>	<i>D</i>	<i>Y</i>	<i>D</i>	<i>Y</i>	<i>D</i>	<i>Y</i>	<i>D</i>
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
$\Sigma$	31.89	1	22.70	0	6.58	1	60.17	2

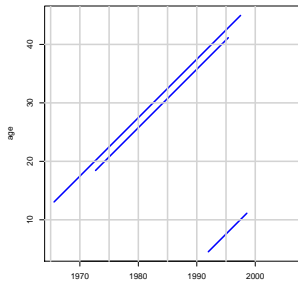
## Time-splitting with R Lexis, splitLexis

```
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 )
```



Splitting the follow-up (rec=split)

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## Your turn now: IHD data

The following exercise is designed to illustrate how follow-up time is subdivided in order to produce the table of events and person-years. Furthermore the aim is to show you that tabulated data and time-split data gives the same results if only age and exposure are used as variables.

We will first analyze frequency records as above (these are almost identical to Table 22.6 in C & H). Next, we shall read the individual records and construct the corresponding table of cases and person-years.

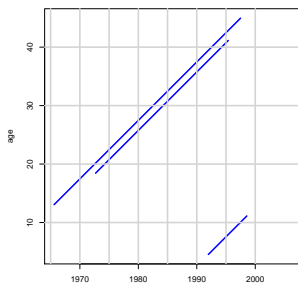
1. Import the program `ihd-lexis-sol.sas` (from the folder <http://bendixcarstensen.com/EpiPhD/F2019/sas>) to the program editor. Run the first part of the program — the part reading the tabulated data and `proc genmod`. Compare with the results from the results table in Clayton & Hills.
2. Next, use the second part of the program to read the individual records from the file `diet.txt`, including the `proc print` and check on the output that it looks reasonable and that you understand what each line in the data represents.

Splitting the follow-up (rec=split)

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## Time-splitting with R Lexis, splitMiltu

```
library( popEpi )
Ls <- splitMulti( Ls, age=seq(0,100,10), per=seq(1900,2000,5),
plot( Ls, col="blue", lwd=3 )
```



Splitting the follow-up (rec=split)

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## Time-splitting with SAS I

3. Now you should import the macro `%Lexis` and use it to split into the age intervals 40–50, 50–60 and 60–70 years:

In order to use this you must first load it from the appropriate folder on the net:

```
* This will list the included code in your log-window ;
options source2 ;
```

```
filename lexispr url "http://BendixCarstensen.com/Lexis/Lexis.sas";
%inc lexispr ;
```

Once you have specified `%inc lexispr ;` and run that line in SAS, SAS will know the macro `%Lexis` and you can use it in the rest of the session.

Splitting the follow-up (rec=split)

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## 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)
- ▶ Likelihood contributions from intervals from one person are **conditionally** independent
- ▶ Likelihood contributions from different persons are independent
- ▶  $\Rightarrow D$  variates can be treated as independent Poisson variates with mean  $\lambda Y$

Splitting the follow-up (rec=split)

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## Time-splitting with SAS II

4. The time-splitting is now done by running the SAS-macro `%Lexis`

A SAS-macro is a piece of SAS-program (normally quite long) where certain small parts of the program can be changed when the program is run. The SAS-convention is that names of such programs start with a "%".

To use the `%Lexis` macro we must specify the follow-up information from the input file:

- ▶ Date of entry into the study — `doe`
- ▶ Date of exit from the study — `dox`
- ▶ Status at exit from the study — `chd` ( 1 if CHD occurred at `dox`, 0 otherwise ).

Moreover, we must decide which timescale to split the data on. In this case we want to split along the scale "current age", i.e. time since date of birth.

Splitting the follow-up (rec=split)

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## What happens when splitting time?

- ▶ **From:** one record per person
- ▶ **To:** many records per person,
- ▶  $\Rightarrow$  allows different rates in different intervals.
- ▶ start point of an interval represented on all time scales:
  - ▶ what is the age here
  - ▶ what date is it here
  - ▶ what is the disease duration here
  - ▶ ...
- ▶  $\Rightarrow$  allows modeling of rates as continuous function of the **timescales** as represented in each interval

Splitting the follow-up (rec=split)

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## Time-splitting with SAS III

5. To this end we must specify:

- ▶ The **origin** of the time-scale, i.e. where the time-scale is 0, in this case date of birth — `dob`.
- ▶ The **intervals** where we want the follow-up grouped, here ages 40–50, 50–60 and 60–70.
- ▶ As a purely technical thing we need to specify the conversion between the **scale** in which time is measured in the input dataset (in this case days) and in the specification of the grouping (in this case years) — 365.25.

In the case of `%Lexis` we must supply these 6 parameters in order to specify how to split time.

Finally we must tell the program where the original data is, where the time-split data has to go, and what the name of the age-variable should be.

Splitting the follow-up (rec=split)

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## Time-splitting with SAS IV

This looks like this (you do not have to write the stuff between the /\*...\*/):

```
%Lexis( data = ihdiv, /* Dataset with original data */
out = ihdsplit, /* Dataset where time-split data go */
entry = doe, /* Date of entry */
exit = dox, /* Date of exit */
fail = chd, /* Event (failure) indicator */
origin = dob, /* Origin of the time-scale */
breaks = 40 to 70 by 10, /* Where to split the time scale */
scale = 365.25, /* Conversion from days to years: */
/* from: scale of entry/exit */
/* to: scale of breaks */
left = agr ); /* The name of the new age-variable */
```

Run this piece of SAS code.

(In the top of the file <http://BendixCarstensen.com/Lexis/Lexis.sas> are some more detailed explanations of how to use %Lexis).

## What happens when splitting time?

We are actually mimicking a **continuous** surveillance of the study population — the smaller the intervals, the closer we get.

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
- ▶ Non-deterministically varying covariates: (current smoking habits, occupational exposure, ...)

## Tabulation of time-split data with SAS I

6. How many records are in the resulting dataset (ihdsplit)
7. Take a look at the resulting data file, for example the first 20 records:

```
proc print data = ihdsplit (obs=20) ;
run ;
```

How does this compare with the the original dataset?

8. Use %PYtab to tabulate IHD-cases and person-years by exposure and age-group. You must first get this from the net as you did with the %Lexis macro:

```
filename pytabpr url "http://BendixCarstensen.com/Lexis/PYtab.sas";
%inc pytabpr ;
```

## 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 — they are all covariates.

## Tabulation of time-split data with SAS II

Once you have imported the macro you can use it:

```
%PYtab( data = ihdsplit,
class = exposure agr,
fail = chd,
risk = risk,
scale = 1000 ) ;
```

Compare with the sums from the table given in the first data step in `ihd-lexis.sas`

## From split to aggregate data

- ▶ Each interval contribute  $d \log(\lambda) - \lambda y$  to the log-likelihood.
- ▶ All intervals with the same set of covariate values (age, exposure, ...) have the same  $\lambda$ .
- ▶ The log-likelihood contribution from these is

$$\sum d \log(\lambda) - \lambda \sum y = D \log(\lambda) - \lambda Y$$

— the same as from **aggregated** data.

- ▶ The log-likelihood is the same for split data and aggregated data — no need to tabulate first.
- ▶ (... except possibly for computing time)

## What about the Cox-model?

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

- ▶ Assumes (the baseline) rate to vary arbitrarily over time
- ▶ — internally in the program, the data is split
- ▶ Time-dependent covariates require multiple records per person
- ▶ Additional time-scales require multiple records per person
- ▶ Main time scale and other time scales modeled differently

## Your turn again:

9. Use `proc genmod` to estimate the effect of age and exposure from the split dataset. How does the estimates compare with those based on the initially tabulated dataset?
10. Add an interaction between age and exposure and check that you get the same test for interaction as with the grouped data.
11. Compare the type 3 likelihood ratio statistic (Chi-square) for the interaction with the deviance of the model without interaction for the grouped data.