Splitting the follow-up
C&H 6

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Department of Biostatistics,
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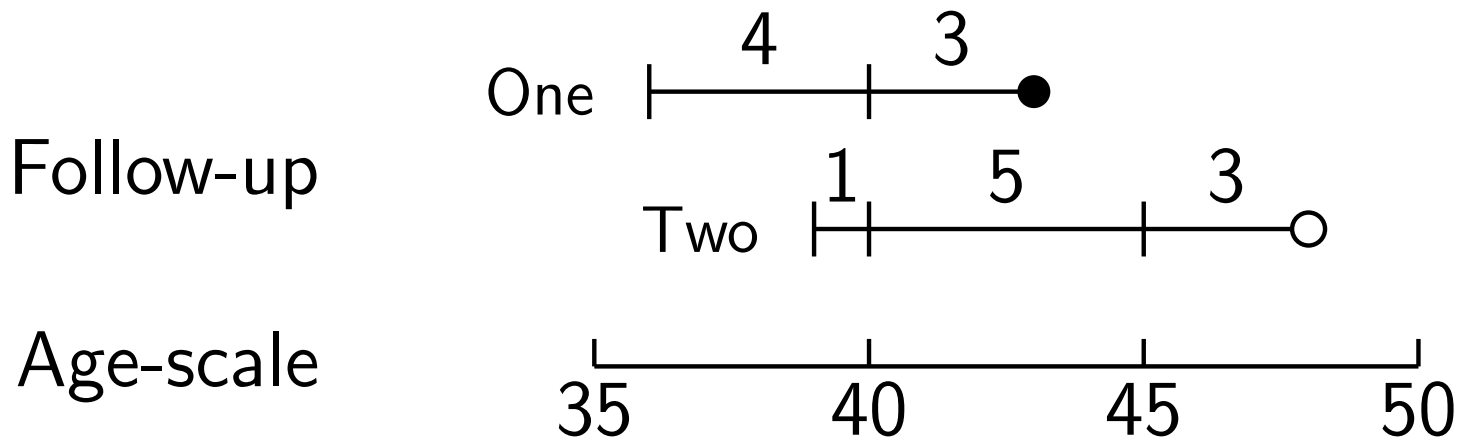
Stratification by age

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.



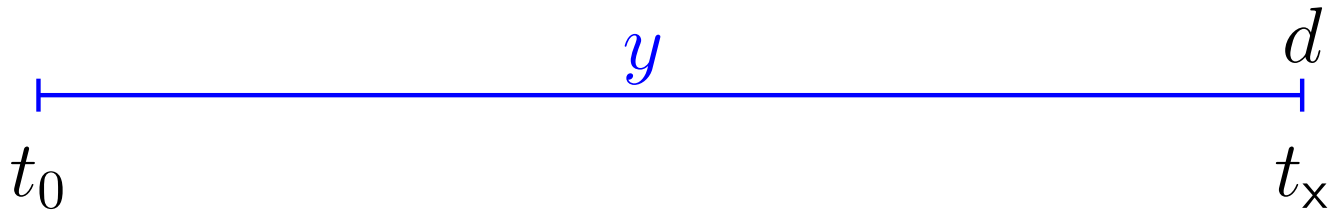
Representation of follow-up data

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.



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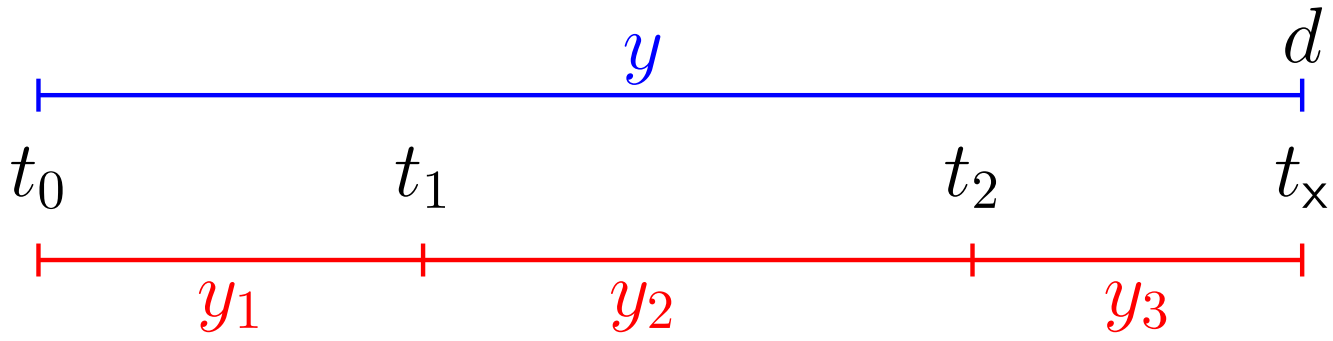
$\mathrm{P}(d \text{ at } t_x \vert \text{entry } t_0)$	$d \log(\lambda) - \lambda y$



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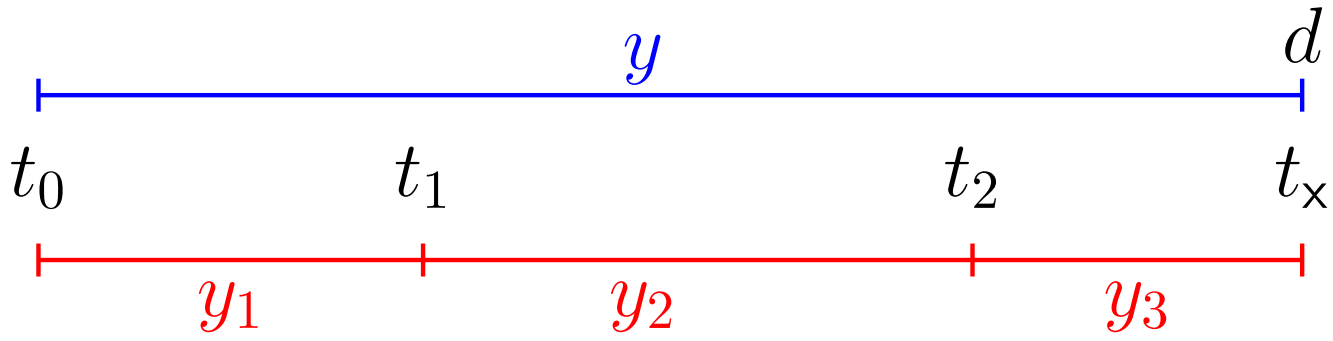

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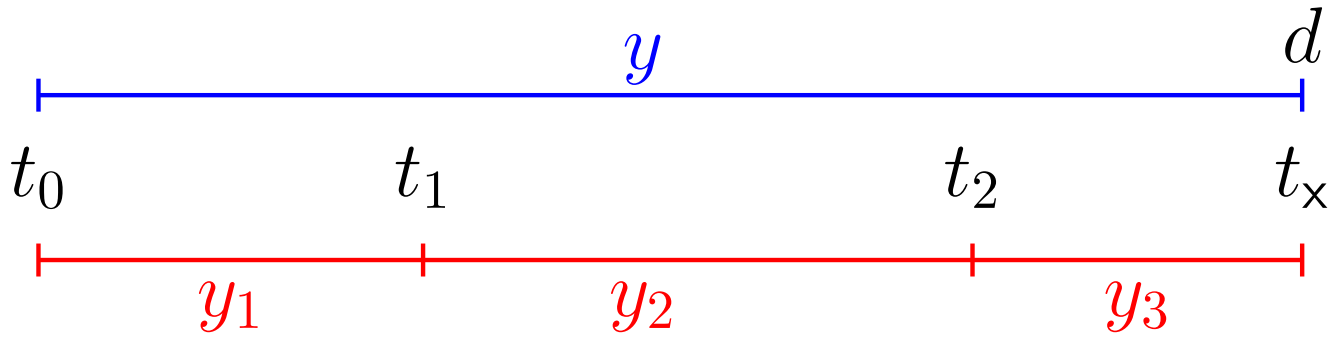

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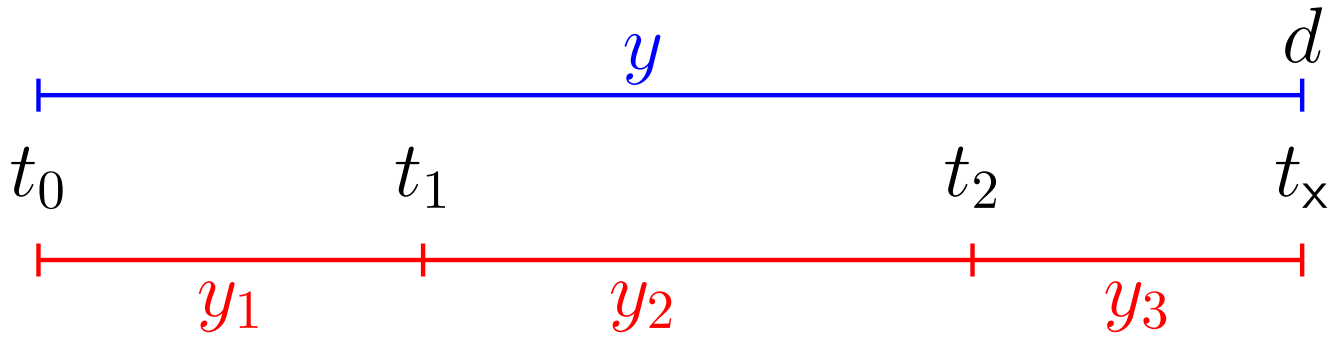

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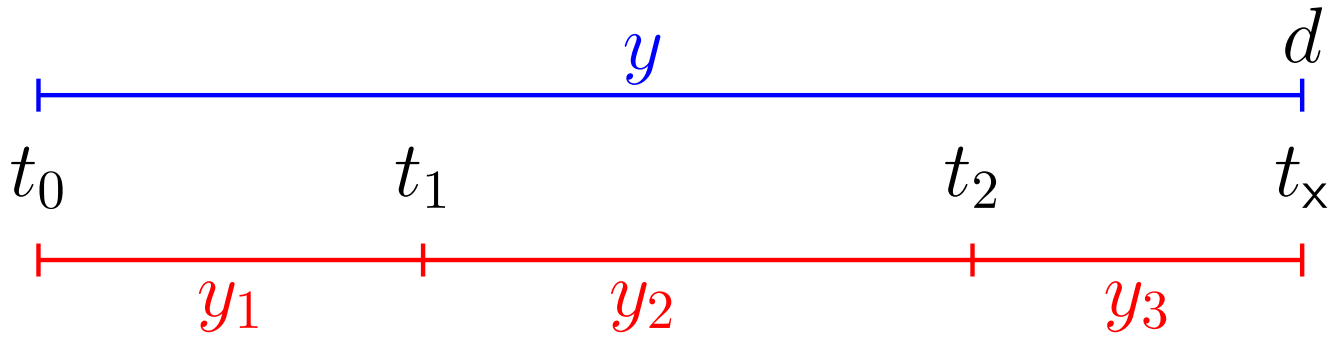

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$$d \log(\lambda) - \lambda y$$

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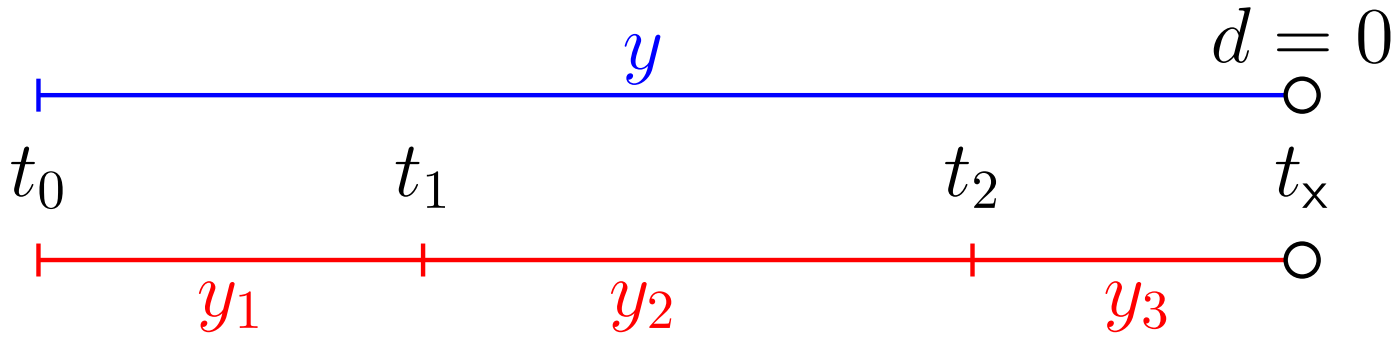

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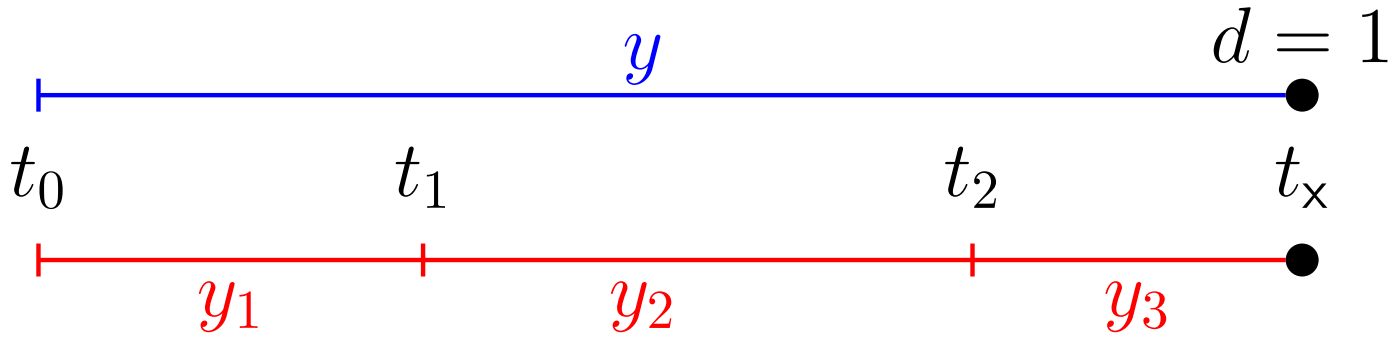

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$\times \mathrm{P}(\text{surv } t_1 \to t_2 \mid \text{entry } t_1)$	$+ 0 \log(\lambda) - \lambda y_2$
$\times \mathrm{P}(\text{event at } t_x \mid \text{entry } t_2)$	$+ 1 \log(\lambda) - \lambda y_3$

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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, 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

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)
```

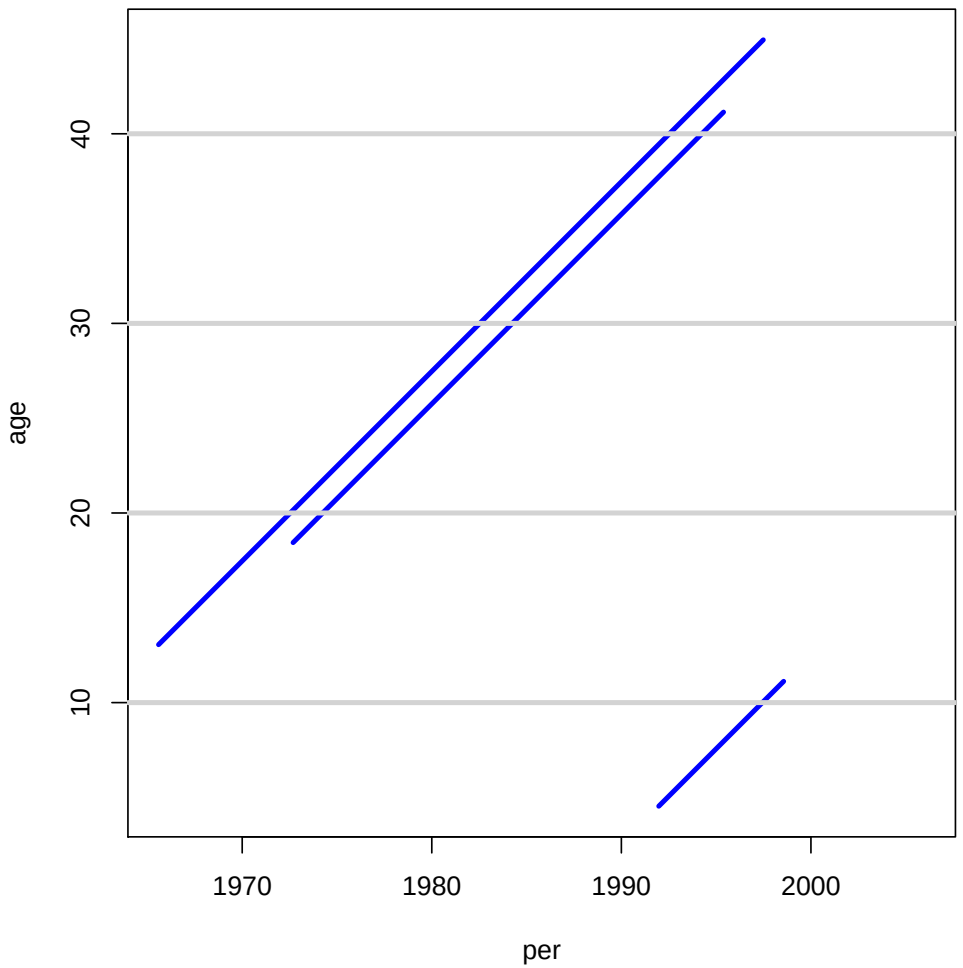
Time-splitting with R Lexis, splitLexis

```
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"
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```

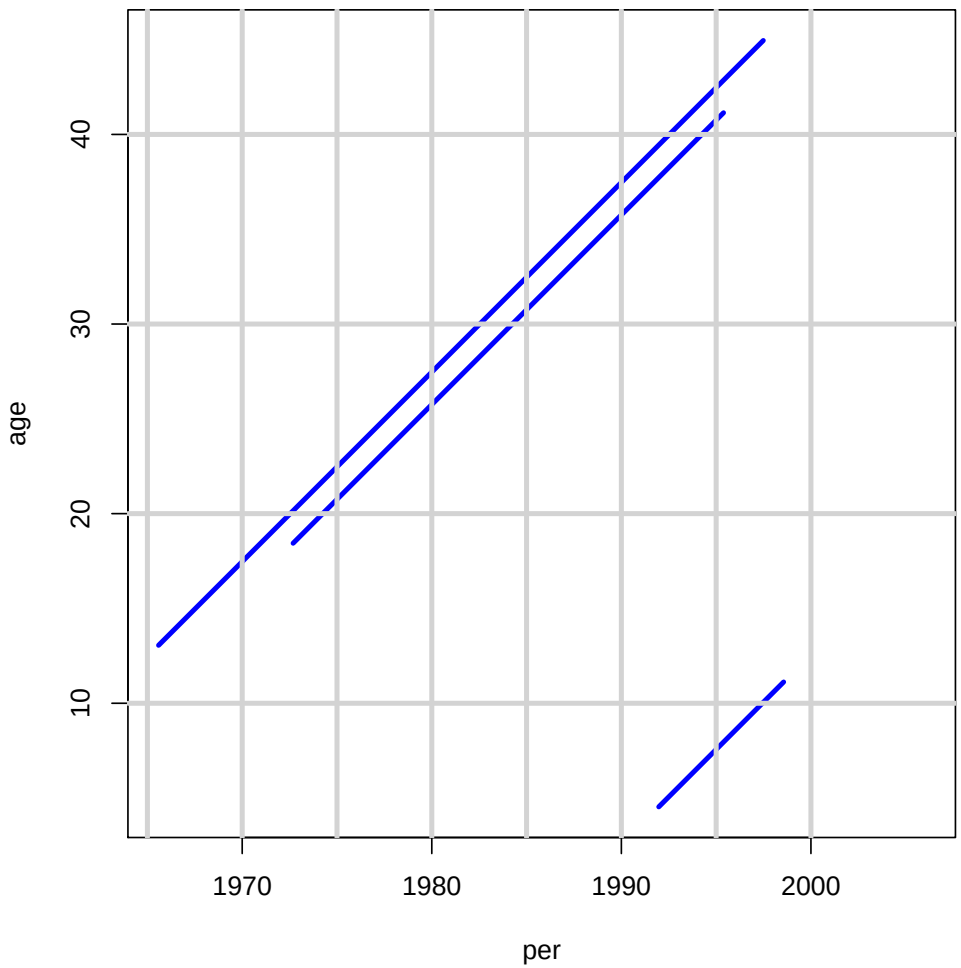

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- **Same** total no. events
- **Same** total follow-up time (PYs)
- Possibility of different rates in different intervals.

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- Additional time-scales require multiple records per person

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- 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, . . .)

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Models for time-split data

Relation to the Cox-model:

$$\begin{aligned}\lambda(t) &= \lambda_0(t)\exp(x_1\beta_1 + x_2\beta_2 + \cdots) \\ &= \exp(\log\big(\lambda_0(t)\big) + x_1\beta_1 + x_2\beta_2 + \cdots) \\ &= \exp(z_1\alpha_1 + z_2\alpha_2 + \cdots + x_1\beta_1 + x_2\beta_2 + \cdots)\end{aligned}$$

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

The baseline hazard — unspecified in the Cox-model — is replaced by a parmetric function, $\exp(z_1\alpha_1 + z_2\alpha_2 + \cdots)$

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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.

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- 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.

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- The event intervals contribute each $D \log \lambda$.

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- 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.

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.

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.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 table xx 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 the data represents.

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 folder on the net:

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

filename lexispr url
 "http://www.biostat.ku.dk/~bxc/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.

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 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.

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.

Time-splitting with SAS IV

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

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

Run this piece of SAS code.

(In the top of the file `http://www.biostat.ku.dk/~bxc/Lexis/Lexis.sas` are some more detailed explanations of how to use `%Lexis`).

Tabulation of time-split data with SAS I

6. How many records are in the resulting dataset (`ihdsplit`)
7. Take at 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://www.biostat.ku.dk/~bxc/Lexis/PYtab.sas";
%inc pytabpr ;
```

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`