

Follow-up data with the Epi package

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```
> library(Epi)
> print( sessionInfo(), l=F )

R version 3.2.3 (2015-12-10)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Ubuntu 14.04.3 LTS

attached base packages:
[1] utils      datasets   graphics  grDevices stats      methods    base

other attached packages:
[1] Epi_1.1.71

loaded via a namespace (and not attached):
[1] cmprsk_2.2-7    MASS_7.3-44     parallel_3.2.3  survival_2.38-3 etm_0.6-2
[7] grid_3.2.3     lattice_0.20-31
```

1 Follow-up data in the *Epi* package

In the *Epi*-package, follow-up data is represented by adding some extra variables to a dataframe. Such a dataframe is called a `Lexis` object. The tools for handling follow-up data then use the structure of this for special plots, tabulations etc.

Follow-up data basically consists of a time of entry, a time of exit and an indication of the status at exit (normally either “alive” or “dead”). Implicitly is also assumed a status *during* the follow-up (usually “alive”).

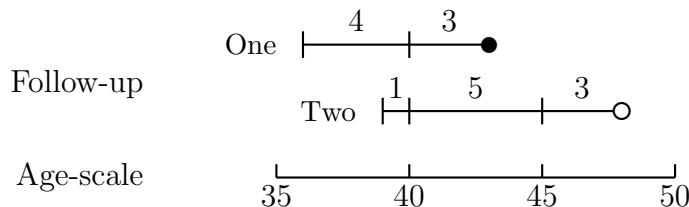


Figure 1: *Follow-up of two persons*

2 Timescales

A timescale is a variable that varies deterministically *within* each person during follow-up, *e.g.*:

- Age
- Calendar time
- Time since treatment

- Time since relapse

All timescales advance at the same pace, so the time followed is the same on all timescales. Therefore, it suffices to use only the entry point on each of the time scale, for example:

- Age at entry.
- Date of entry.
- Time since treatment (*at* treatment this is 0).
- Time since relapse (*at* relapse this is 0)..

In the Epi package, follow-up in a cohort is represented in a **Lexis** object. A **Lexis** object is a dataframe with a bit of extra structure representing the follow-up. For the **nickel** data we would construct a **Lexis** object by:

```
> data( nickel )
> nicL <- Lexis( entry = list( per=agein+dob,
+                               age=agein,
+                               tfh=agein-age1st ),
+                     exit = list( age=ageout ),
+                     exit.status = ( icd %in% c(162,163) )*1,
+                     data = nickel )
```

The **entry** argument is a *named* list with the entry points on each of the timescales we want to use. It defines the names of the timescales and the entry points. The **exit** argument gives the exit time on *one* of the timescales, so the name of the element in this list must match one of the names of the **entry** list. This is sufficient, because the follow-up time on all time scales is the same, in this case **ageout** - **agein**. Now take a look at the result:

```
> str( nickel )

'data.frame':      679 obs. of  7 variables:
 $ id      : num  3 4 6 8 9 10 15 16 17 18 ...
 $ icd     : num  0 162 163 527 150 163 334 160 420 12 ...
 $ exposure: num  5 5 10 9 0 2 0 0.5 0 0 ...
 $ dob     : num  1889 1886 1881 1886 1880 ...
 $ age1st   : num  17.5 23.2 25.2 24.7 30 ...
 $ agein    : num  45.2 48.3 53 47.9 54.7 ...
 $ ageout   : num  93 63.3 54.2 69.7 76.8 ...

> str( nicL )

Classes 'Lexis' and 'data.frame':      679 obs. of  14 variables:
 $ per      : num  1934 1934 1934 1934 1934 ...
 $ age      : num  45.2 48.3 53 47.9 54.7 ...
```

```
$ tfh      : num  27.7 25.1 27.7 23.2 24.8 ...
$ lex.dur : num  47.75 15 1.17 21.77 22.1 ...
$ lex.Cst : num  0 0 0 0 0 0 0 0 0 ...
$ lex.Xst : num  0 1 1 0 0 1 0 0 0 0 ...
$ lex.id  : int  1 2 3 4 5 6 7 8 9 10 ...
$ id       : num  3 4 6 8 9 10 15 16 17 18 ...
$ icd      : num  0 162 163 527 150 163 334 160 420 12 ...
$ exposure: num  5 5 10 9 0 2 0 0.5 0 0 ...
$ dob      : num  1889 1886 1881 1886 1880 ...
$ age1st   : num  17.5 23.2 25.2 24.7 30 ...
$ agein    : num  45.2 48.3 53 47.9 54.7 ...
$ ageout   : num  93 63.3 54.2 69.7 76.8 ...
- attr(*, "time.scales")= chr  "per" "age" "tfh"
- attr(*, "time.since")= chr  "" "" ""
- attr(*, "breaks")=List of 3
..$ per: NULL
..$ age: NULL
..$ tfh: NULL

> head( nicL )

      per     age     tfh lex.dur lex.Cst lex.Xst lex.id id icd exposure      dob a
1 1934.246 45.2273 27.7465 47.7535      0      0      1  3  0      5 1889.019 17
2 1934.246 48.2684 25.0820 15.0028      0      1      2  4 162      5 1885.978 23
3 1934.246 52.9917 27.7465  1.1727      0      1      3  6 163     10 1881.255 25
4 1934.246 47.9067 23.1861 21.7727      0      0      4  8 527      9 1886.340 24
5 1934.246 54.7465 24.7890 22.0977      0      0      5  9 150      0 1879.500 29
6 1934.246 44.3314 23.0437 18.2099      0      1      6 10 163      2 1889.915 21

      ageout
1 92.9808
2 63.2712
3 54.1644
4 69.6794
5 76.8442
6 62.5413
```

The **Lexis** object **nicL** has a variable for each timescale which is the entry point on this timescale. The follow-up time is in the variable **lex.dur** (**duration**).

There is a **summary** function for Lexis objects that list the number of transitions and records as well as the total follow-up time:

```
> summary( nicL )

Transitions:
      To
From 0 1 Records: Events: Risk time: Persons:
      0 542 137      679      137 15348.06      679
```

We defined the exit status to be death from lung cancer (ICD7 162,163), i.e. this variable is 1 if follow-up ended with a death from this cause. If follow-up ended alive or by death from another cause, the exit status is coded 0, i.e. as a censoring.

Note that the exit status is in the variable `lex.Xst` (eXit status). The variable `lex.Cst` is the state where the follow-up takes place (**C**urrent **s**tatus), in this case 0 (alive).

It is possible to get a visualization of the follow-up along the timescales chosen by using the `plot` method for `Lexis` objects. `nicL` is an object of *class Lexis*, so using the function `plot()` on it means that **R** will look for the function `plot.Lexis` and use this function.

```
> plot( nicL )
```

The function allows a lot of control over the output, and a `points.Lexis` function allows plotting of the endpoints of follow-up:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plot( nicL, 1:2, lwd=1, col=c("blue","red")[(nicL$exp>0)+1],
+       grid=TRUE, lty.grid=1, col.grid=gray(0.7),
+       xlim=1900+c(0,90), xaxs="i",
+       ylim= 10+c(0,90), yaxs="i", las=1 )
> points( nicL, 1:2, pch=c(NA,3)[nicL$lex.Xst+1],
+           col="lightgray", lwd=3, cex=1.5 )
> points( nicL, 1:2, pch=c(NA,3)[nicL$lex.Xst+1],
+           col=c("blue","red")[(nicL$exp>0)+1], lwd=1, cex=1.5 )
```

The results of these two plotting commands are in figure 2.

3 Splitting the follow-up time along a timescale

The follow-up time in a cohort can be subdivided by for example current age. This is achieved by the `splitLexis` (note that it is *not* called `split.Lexis`). This requires that the timescale and the breakpoints on this timescale are supplied. Try:

```
> nicS1 <- splitLexis( nicL, "age", breaks=seq(0,100,10) )
> summary( nicL )
```

Transitions:

	To	From	Records:	Events:	Risk time:	Persons:
		0	542	137	679	137
						15348.06
						679

```
> summary( nicS1 )
```

Transitions:

	To	From	Records:	Events:	Risk time:	Persons:
		0	2073	137	2210	137
						15348.06
						679

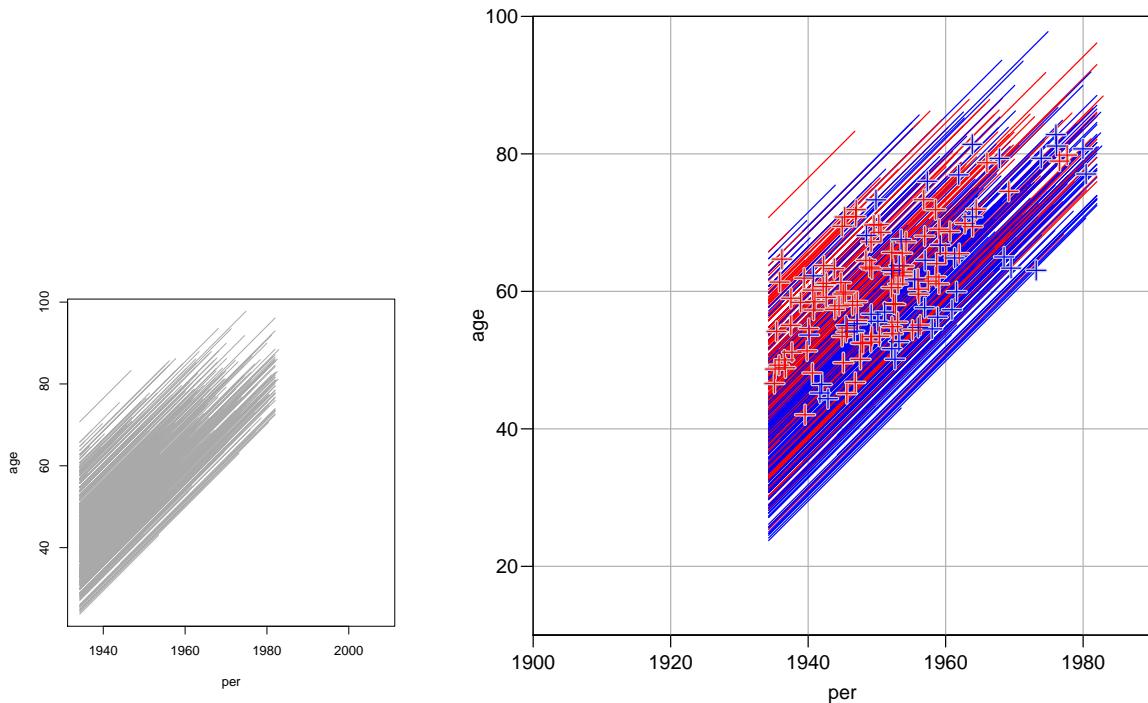


Figure 2: Lexis diagram of the *nickel* dataset, left panel the default version, the right one with bells and whistles. The red lines are for persons with $\text{exposure} > 0$, so it is pretty evident that the oldest ones are the exposed part of the cohort.

So we see that the number of events and the amount of follow-up is the same in the two datasets; only the number of records differ.

To see how records are split for each individual, it is useful to list the results for a few individuals:

```
> round( subset( nicS1, id %in% 8:10 ), 2 )
```

	lex.id	per	age	tfh	lex.dur	lex.Cst	lex.Xst	id	icd	exposure	dob	age1st
11	4	1934.25	47.91	23.19	2.09	0	0	8	527	9	1886.34	24.72
12	4	1936.34	50.00	25.28	10.00	0	0	8	527	9	1886.34	24.72
13	4	1946.34	60.00	35.28	9.68	0	0	8	527	9	1886.34	24.72
14	5	1934.25	54.75	24.79	5.25	0	0	9	150	0	1879.50	29.96
15	5	1939.50	60.00	30.04	10.00	0	0	9	150	0	1879.50	29.96
16	5	1949.50	70.00	40.04	6.84	0	0	9	150	0	1879.50	29.96
17	6	1934.25	44.33	23.04	5.67	0	0	10	163	2	1889.91	21.29
18	6	1939.91	50.00	28.71	10.00	0	0	10	163	2	1889.91	21.29
19	6	1949.91	60.00	38.71	2.54	0	1	10	163	2	1889.91	21.29

The resulting object, *nicS1*, is again a `Lexis` object, and so follow-up may be split further along another timescale. Try this and list the results for individuals 8, 9 and 10 again:

```
> nicS2 <- splitLexis( nicS1, "tfh", breaks=c(0,1,5,10,20,30,100) )
> round( subset( nicS2, id %in% 8:10 ), 2 )
```

	lex.id	per	age	tfh	lex.dur	lex.Cst	lex.Xst	id	icd	exposure	dob	age1st
13	4	1934.25	47.91	23.19	2.09	0	0	8	527	9	1886.34	24.72
14	4	1936.34	50.00	25.28	4.72	0	0	8	527	9	1886.34	24.72
15	4	1941.06	54.72	30.00	5.28	0	0	8	527	9	1886.34	24.72
16	4	1946.34	60.00	35.28	9.68	0	0	8	527	9	1886.34	24.72
17	5	1934.25	54.75	24.79	5.21	0	0	9	150	0	1879.50	29.96
18	5	1939.46	59.96	30.00	0.04	0	0	9	150	0	1879.50	29.96
19	5	1939.50	60.00	30.04	10.00	0	0	9	150	0	1879.50	29.96
20	5	1949.50	70.00	40.04	6.84	0	0	9	150	0	1879.50	29.96
21	6	1934.25	44.33	23.04	5.67	0	0	10	163	2	1889.91	21.29
22	6	1939.91	50.00	28.71	1.29	0	0	10	163	2	1889.91	21.29
23	6	1941.20	51.29	30.00	8.71	0	0	10	163	2	1889.91	21.29
24	6	1949.91	60.00	38.71	2.54	0	1	10	163	2	1889.91	21.29

If we want to model the effect of these timescales we will for each interval use either the value of the left endpoint in each interval or the middle. There is a function `timeBand` which returns these. Try:

```
> timeBand( nicS2, "age", "middle" )[1:20]
[1] 45 45 55 65 75 85 95 45 55 55 65 55 45 55 55 65 55 55 65 75

> # For nice printing and column labelling use the data.frame() function:
> data.frame( nicS2[,c("id","lex.id","per","age","tfh","lex.dur")],
+             mid.age=timeBand( nicS2, "age", "middle" ),
+             mid.tfh=timeBand( nicS2, "tfh", "middle" ) )[1:20,]

  id lex.id      per      age      tfh lex.dur mid.age mid.tfh
1  3    1 1934.246 45.2273 27.7465  2.2535     45     25
2  3    1 1936.500 47.4808 30.0000  2.5192     45     65
3  3    1 1939.019 50.0000 32.5192 10.0000     55     65
4  3    1 1949.019 60.0000 42.5192 10.0000     65     65
5  3    1 1959.019 70.0000 52.5192 10.0000     75     65
6  3    1 1969.019 80.0000 62.5192 10.0000     85     65
7  3    1 1979.019 90.0000 72.5192  2.9808     95     65
8  4    2 1934.246 48.2684 25.0820  1.7316     45     25
9  4    2 1935.978 50.0000 26.8136  3.1864     55     25
10 4    2 1939.164 53.1864 30.0000  6.8136     55     65
11 4    2 1945.978 60.0000 36.8136  3.2712     65     65
12 6    3 1934.246 52.9917 27.7465  1.1727     55     25
13 8    4 1934.246 47.9067 23.1861  2.0933     45     25
14 8    4 1936.340 50.0000 25.2794  4.7206     55     25
15 8    4 1941.060 54.7206 30.0000  5.2794     55     65
16 8    4 1946.340 60.0000 35.2794  9.6794     65     65
17 9    5 1934.246 54.7465 24.7890  5.2110     55     25
18 9    5 1939.457 59.9575 30.0000  0.0425     55     65
19 9    5 1939.500 60.0000 30.0425 10.0000     65     65
20 9    5 1949.500 70.0000 40.0425  6.8442     75     65
```

Note that these are the midpoints of the intervals defined by `breaks=`, *not* the midpoints of the actual follow-up intervals. This is because the variable to be used in modelling must be independent of the censoring and mortality pattern — it should only depend on the chosen grouping of the timescale.

4 Splitting time at a specific date

If we have a recording of the date of a specific event as for example recovery or relapse, we may classify follow-up time as being before or after this intermediate event. This is achieved with the function `cutLexis`, which takes three arguments: the time point, the timescale, and the value of the (new) state following the date.

Now we define the age for the nickel workers where the cumulative exposure exceeds 50 exposure years:

```
> subset( nicL, id %in% 8:10 )

      per      age      tfh lex.dur lex.Cst lex.Xst lex.id id icd exposure      dob a
4 1934.246 47.9067 23.1861 21.7727      0      0      4  8 527      9 1886.340 24
5 1934.246 54.7465 24.7890 22.0977      0      0      5  9 150      0 1879.500 29
6 1934.246 44.3314 23.0437 18.2099      0      1      6 10 163      2 1889.915 21

      ageout
4 69.6794
5 76.8442
6 62.5413

> agehi <- nicL$age1st + 50 / nicL$exposure
> nicC <- cutLexis( data=nicL, cut=agehi, timescale="age",
+                      new.state=2, precursor.states=0 )
> subset( nicC, id %in% 8:10 )

      per      age      tfh lex.dur lex.Cst lex.Xst lex.id id icd exposure      dob
4100 1934.246 47.9067 23.1861 21.7727      2      2      4  8 527      9 1886.340
5     1934.246 54.7465 24.7890 22.0977      0      0      5  9 150      0 1879.500
6     1934.246 44.3314 23.0437  1.9563      0      2      6 10 163      2 1889.915
680 1936.203 46.2877 25.0000 16.2536      2      1      6 10 163      2 1889.915

      agein ageout
4100 47.9067 69.6794
5     54.7465 76.8442
6     44.3314 62.5413
680 44.3314 62.5413
```

(The `precursor.states=` argument is explained below). Note that individual 6 has had his follow-up split at age 25 where 50 exposure-years were attained. This could also have been achieved in the split dataset `nicS2` instead of `nicL`, try:

```
> subset( nicS2, id %in% 8:10 )
```

```

lex.id      per      age      tfh lex.dur lex.Cst lex.Xst id icd exposure      dob
13        4 1934.246 47.9067 23.1861  2.0933      0      0 8 527      9 1886.340 2
14        4 1936.340 50.0000 25.2794  4.7206      0      0 8 527      9 1886.340 2
15        4 1941.060 54.7206 30.0000  5.2794      0      0 8 527      9 1886.340 2
16        4 1946.340 60.0000 35.2794  9.6794      0      0 8 527      9 1886.340 2
17        5 1934.246 54.7465 24.7890  5.2110      0      0 9 150      0 1879.500 2
18        5 1939.457 59.9575 30.0000  0.0425      0      0 9 150      0 1879.500 2
19        5 1939.500 60.0000 30.0425 10.0000      0      0 9 150      0 1879.500 2
20        5 1949.500 70.0000 40.0425  6.8442      0      0 9 150      0 1879.500 2
21        6 1934.246 44.3314 23.0437  5.6686      0      0 10 163     2 1889.915 2
22        6 1939.915 50.0000 28.7123  1.2877      0      0 10 163     2 1889.915 2
23        6 1941.203 51.2877 30.0000  8.7123      0      0 10 163     2 1889.915 2
24        6 1949.915 60.0000 38.7123  2.5413      0      1 10 163     2 1889.915 2

ageout
13 69.6794
14 69.6794
15 69.6794
16 69.6794
17 76.8442
18 76.8442
19 76.8442
20 76.8442
21 62.5413
22 62.5413
23 62.5413
24 62.5413

> agehi <- nicS2$age1st + 50 / nicS2$exposure
> nicS2C <- cutLexis( data=nicS2, cut=agehi, timescale="age",
+                         new.state=2, precursor.states=0 )
> subset( nicS2C, id %in% 8:10 )

lex.id      per      age      tfh lex.dur lex.Cst lex.Xst id icd exposure      dob
3142        4 1934.246 47.9067 23.1861  2.0933      2      2 8 527      9 1886.340 2
3143        4 1936.340 50.0000 25.2794  4.7206      2      2 8 527      9 1886.340 2
3144        4 1941.060 54.7206 30.0000  5.2794      2      2 8 527      9 1886.340 2
3145        4 1946.340 60.0000 35.2794  9.6794      2      2 8 527      9 1886.340 2
17        5 1934.246 54.7465 24.7890  5.2110      0      0 9 150      0 1879.500 2
18        5 1939.457 59.9575 30.0000  0.0425      0      0 9 150      0 1879.500 2
19        5 1939.500 60.0000 30.0425 10.0000      0      0 9 150      0 1879.500 2
20        5 1949.500 70.0000 40.0425  6.8442      0      0 9 150      0 1879.500 2
21        6 1934.246 44.3314 23.0437  1.9563      0      2 10 163     2 1889.915 2
3150        6 1936.203 46.2877 25.0000  3.7123      2      2 10 163     2 1889.915 2
3151        6 1939.915 50.0000 28.7123  1.2877      2      2 10 163     2 1889.915 2
3152        6 1941.203 51.2877 30.0000  8.7123      2      2 10 163     2 1889.915 2
3153        6 1949.915 60.0000 38.7123  2.5413      2      1 10 163     2 1889.915 2

```

```

      agein  ageout
3142 47.9067 69.6794
3143 47.9067 69.6794
3144 47.9067 69.6794
3145 47.9067 69.6794
17   54.7465 76.8442
18   54.7465 76.8442
19   54.7465 76.8442
20   54.7465 76.8442
21   44.3314 62.5413
3150 44.3314 62.5413
3151 44.3314 62.5413
3152 44.3314 62.5413
3153 44.3314 62.5413

```

Note that follow-up subsequent to the event is classified as being in state 2, but that the final transition to state 1 (death from lung cancer) is preserved. This is the point of the `precursor.states=` argument. It names the states (in this case 0, “Alive”) that will be over-written by `new.state` (in this case state 2, “High exposure”). Clearly, state 1 (“Dead”) should not be updated even if it is after the time where the persons moves to state 2. In other words, only state 0 is a precursor to state 2, state 1 is always subsequent to state 2.

Note if the intermediate event is to be used as a time-dependent variable in a Cox-model, then `lex.Cst` should be used as the time-dependent variable, and `lex.Xst==1` as the event.

5 Competing risks — multiple types of events

If we want to consider death from lung cancer and death from other causes as separate events we can code these as for example 1 and 2.

```

> data( nickel )
> nicL <- Lexis( entry = list( per=agein+dob,
+                               age=agein,
+                               tfh=agein-age1st ),
+                   exit = list( age=ageout ),
+                   exit.status = ( icd > 0 ) + ( icd %in% c(162,163) ),
+                   data = nickel )
> summary( nicL )

```

Transitions:

To	From 0	1	2	Records:	Events:	Risk time:	Persons:	
	0 47	495	137		679	632	15348.06	679

```
> subset( nicL, id %in% 8:10 )
```

If we want to label the states, we can enter the names of these in the `states` parameter, try for example:

```

> nicL <- Lexis( entry = list( per=agein+dob,
+                               age=agein,
+                               tfh=agein-age1st ),
+                     exit = list( age=ageout ),
+                     exit.status = ( icd > 0 ) + ( icd %in% c(162,163) ),
+                     data = nickel,
+                     states = c("Alive", "D.oth", "D.lung") )
> summary( nicL )

```

Transitions:

To

From Alive D.oth D.lung Records: Events: Risk time: Persons:
 Alive 47 495 137 679 632 15348.06 679

Note that the `Lexis` function automatically assumes that all persons enter in the first level (given in the `states=` argument)

When we cut at a date as in this case, the date where cumulative exposure exceeds 50 exposure-years, we get the follow-up *after* the date classified as being in the new state if the exit (`lex.Xst`) was to a state we defined as one of the `precursor.states`:

```

> nicL$agehi <- nicL$age1st + 50 / nicL$exposure
> nicC <- cutLexis( data = nicL,
+                     cut = nicL$agehi,
+                     timescale = "age",
+                     new.state = "HiExp",
+                     precursor.states = "Alive" )
> subset( nicC, id %in% 8:10 )

```

```
4100 47.9067 69.6794 30.27616
5    54.7465 76.8442      Inf
6    44.3314 62.5413 46.28770
680 44.3314 62.5413 46.28770

> summary( nicC, scale=1000 )
```

Transitions:

To	From	Alive	HiExp	D.oth	D.lung	Records:	Events:	Risk	time:	Persons:
Alive	Alive	39	83	279	65	466	427	10.77		466
HiExp	HiExp	0	8	216	72	296	288	4.58		296
	Sum	39	91	495	137	762	715	15.35		679

Note that the persons-years is the same, but that the number of events has changed. This is because events are now defined as any transition from alive, including the transitions to HiExp.

Also note that (so far) it is necessary to specify the variable with the cutpoints in full, using only `cut=agehi` would give an error.

Subdivision of existing states

It may be of interest to subdivide the states following the intermediate event according to whether the event has occurred or not. That is done by the argument `split.states=TRUE`.

Moreover, it will also often be of interest to introduce a new timescale indicating the time since intermediate event. This can be done by the argument `new.scale=TRUE`, alternatively `new.scale="tfevent"`, as illustrated here:

```
> nicC <- cutLexis( data = nicL,
+                     cut = nicL$agehi,
+                     timescale = "age",
+                     new.state = "Hi",
+                     split.states=TRUE, new.scale=TRUE,
+                     precursor.states = "Alive" )
> subset( nicC, id %in% 8:10 )

      per      age      tfh   Hi.dur lex.dur lex.Cst    lex.Xst lex.id id icd expos
4100 1934.246 47.9067 23.1861 17.63054 21.7727      Hi D.oth(Hi)     4  8 527
5    1934.246 54.7465 24.7890        NA 22.0977    Alive      D.oth     5  9 150
6    1934.246 44.3314 23.0437        NA  1.9563    Alive          Hi     6 10 163
680 1936.203 46.2877 25.0000  0.00000 16.2536      Hi D.lung(Hi)     6 10 163
                    age1st  agein  ageout  agehi
4100 24.7206 47.9067 69.6794 30.27616
5    29.9575 54.7465 76.8442      Inf
6    21.2877 44.3314 62.5413 46.28770
680 21.2877 44.3314 62.5413 46.28770
```

```
> summary( nicC, scale=1000 )
```

Transitions:

From	Alive	Hi	D.oth	D.lung	D.lung(Hi)	D.oth(Hi)	Records:	Events:	Risk	time:	Per
To											
Alive	39	83	279	65	0	0	466	427		10.77	
Hi	0	8	0	0	72	216	296	288		4.58	
Sum	39	91	279	65	72	216	762	715		15.35	

6 Multiple events of the same type (recurrent events)

Sometimes more events of the same type are recorded for each person and one would then like to count these and put follow-up time in states accordingly. Essentially, each set of cutpoints represents progressions from one state to the next. Therefore the states should be numbered, and the numbering of states subsequently occupied be increased accordingly.

This is a behaviour different from the one outlined above, and it is achieved by the argument `count=TRUE` to `cutLexis`. When `count` is set to TRUE, the value of the arguments `new.state` and `precursor.states` are ignored. Actually, when using the argument `count=TRUE`, the function `countLexis` is called, so an alternative is to use this directly.