

Follow-up data with the Epi package

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```

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

R version 3.3.1 (2016-06-21)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Ubuntu 14.04.5 LTS

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

other attached packages:
[1] Epi_2.7

loaded via a namespace (and not attached):
 [1] cmprsk_2.2-7      MASS_7.3-45      Matrix_1.2-6     plyr_1.8.4
 [5] parallel_3.3.1    tools_3.3.1      survival_2.39-5  etm_0.6-2
 [9] Rcpp_0.12.5       splines_3.3.1    grid_3.3.1       numDeriv_2014.2-1
[13] lattice_0.20-33

```

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”).

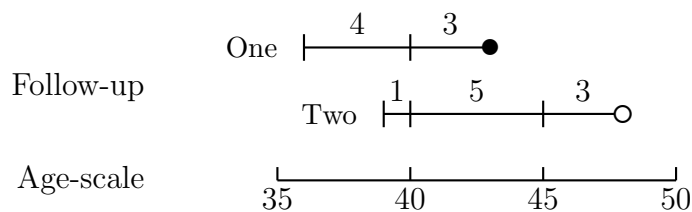


Figure 1: *Follow-up of two persons*

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 neames 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 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
1	1934.246	45.2273	27.7465	47.7535	0	0	1	3	0	5
2	1934.246	48.2684	25.0820	15.0028	0	1	2	4	162	5
3	1934.246	52.9917	27.7465	1.1727	0	1	3	6	163	10
4	1934.246	47.9067	23.1861	21.7727	0	0	4	8	527	9
5	1934.246	54.7465	24.7890	22.0977	0	0	5	9	150	0
6	1934.246	44.3314	23.0437	18.2099	0	1	6	10	163	2
	dob	age1st	agein	ageout						
1	1889.019	17.4808	45.2273	92.9808						
2	1885.978	23.1864	48.2684	63.2712						
3	1881.255	25.2452	52.9917	54.1644						
4	1886.340	24.7206	47.9067	69.6794						
5	1879.500	29.9575	54.7465	76.8442						
6	1889.915	21.2877	44.3314	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` (**d**uration).

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	0	1	Records:	Events:	Risk time:	Persons:
	0	542 137	679	137	15348.06	679

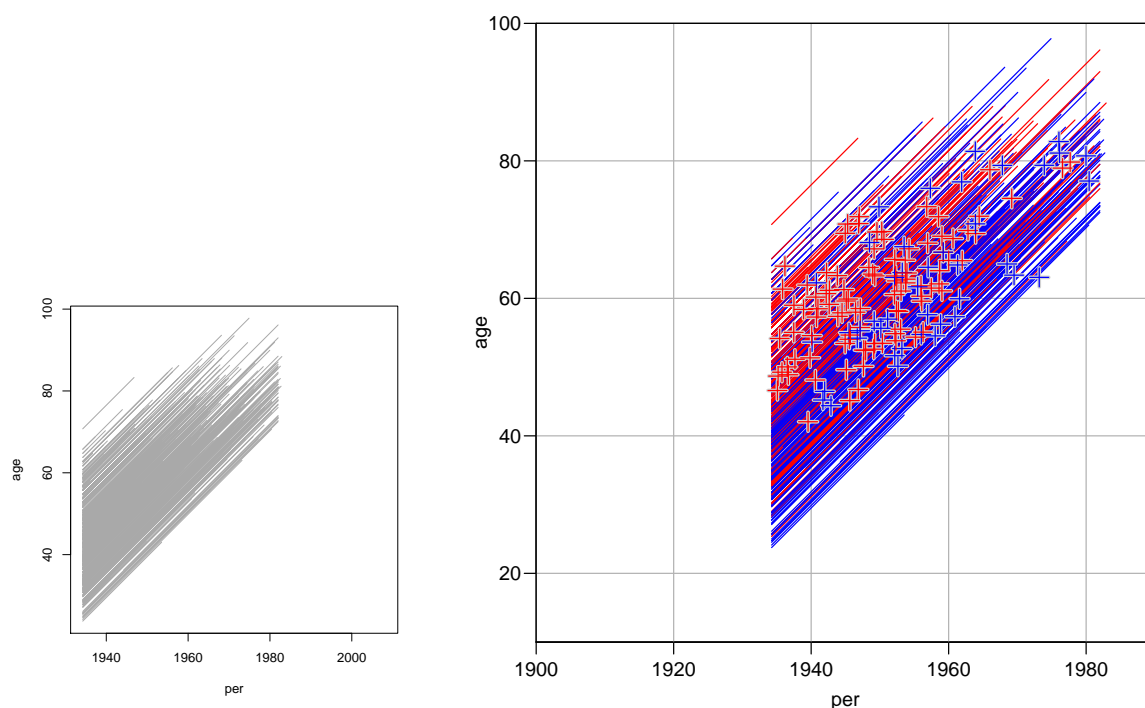


Figure 2: Lexis diagram of the *nickel* dataset, left panel the default version, the right one with bells and whistles. The red lines are for persons with $\text{exposure} > 0$, so it is pretty evident that the oldest ones are the exposed part of the cohort.

```
> summary( nicS1 )
```

Transitions:

To

```
From  0  1  Records:  Events: Risk time:  Persons:
      0 2073 137      2210      137  15348.06      679
```

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
11	4	1934.25	47.91	23.19	2.09	0	0	8	527	9	1886.34
12	4	1936.34	50.00	25.28	10.00	0	0	8	527	9	1886.34
13	4	1946.34	60.00	35.28	9.68	0	0	8	527	9	1886.34
14	5	1934.25	54.75	24.79	5.25	0	0	9	150	0	1879.50
15	5	1939.50	60.00	30.04	10.00	0	0	9	150	0	1879.50
16	5	1949.50	70.00	40.04	6.84	0	0	9	150	0	1879.50
17	6	1934.25	44.33	23.04	5.67	0	0	10	163	2	1889.91

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 of 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 vorkers 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
4	1934.246	47.9067	23.1861	21.7727	0	0	4	8	527	9
5	1934.246	54.7465	24.7890	22.0977	0	0	5	9	150	0
6	1934.246	44.3314	23.0437	18.2099	0	1	6	10	163	2
	dob	age1st	agein	ageout						
4	1886.340	24.7206	47.9067	69.6794						
5	1879.500	29.9575	54.7465	76.8442						
6	1889.915	21.2877	44.3314	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
683	1934.246	47.9067	23.1861	21.7727	2	2	4	8	527	9
5	1934.246	54.7465	24.7890	22.0977	0	0	5	9	150	0
6	1934.246	44.3314	23.0437	1.9563	0	2	6	10	163	2
685	1936.203	46.2877	25.0000	16.2536	2	1	6	10	163	2
	dob	age1st	agein	ageout						
683	1886.340	24.7206	47.9067	69.6794						
5	1879.500	29.9575	54.7465	76.8442						
6	1889.915	21.2877	44.3314	62.5413						
685	1889.915	21.2877	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
13	4	1934.246	47.9067	23.1861	2.0933	0	0	8	527	9
14	4	1936.340	50.0000	25.2794	4.7206	0	0	8	527	9
15	4	1941.060	54.7206	30.0000	5.2794	0	0	8	527	9
16	4	1946.340	60.0000	35.2794	9.6794	0	0	8	527	9
17	5	1934.246	54.7465	24.7890	5.2110	0	0	9	150	0
18	5	1939.457	59.9575	30.0000	0.0425	0	0	9	150	0
19	5	1939.500	60.0000	30.0425	10.0000	0	0	9	150	0
20	5	1949.500	70.0000	40.0425	6.8442	0	0	9	150	0
21	6	1934.246	44.3314	23.0437	5.6686	0	0	10	163	2
22	6	1939.915	50.0000	28.7123	1.2877	0	0	10	163	2

```

23      6 1941.203 51.2877 30.0000 8.7123      0      0 10 163      2
24      6 1949.915 60.0000 38.7123 2.5413      0      1 10 163      2
      dob age1st  agein  ageout
13 1886.340 24.7206 47.9067 69.6794
14 1886.340 24.7206 47.9067 69.6794
15 1886.340 24.7206 47.9067 69.6794
16 1886.340 24.7206 47.9067 69.6794
17 1879.500 29.9575 54.7465 76.8442
18 1879.500 29.9575 54.7465 76.8442
19 1879.500 29.9575 54.7465 76.8442
20 1879.500 29.9575 54.7465 76.8442
21 1889.915 21.2877 44.3314 62.5413
22 1889.915 21.2877 44.3314 62.5413
23 1889.915 21.2877 44.3314 62.5413
24 1889.915 21.2877 44.3314 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
3142      4 1934.246 47.9067 23.1861 2.0933      2      2 8 527      9
3143      4 1936.340 50.0000 25.2794 4.7206      2      2 8 527      9
3144      4 1941.060 54.7206 30.0000 5.2794      2      2 8 527      9
3145      4 1946.340 60.0000 35.2794 9.6794      2      2 8 527      9
17      5 1934.246 54.7465 24.7890 5.2110      0      0 9 150      0
18      5 1939.457 59.9575 30.0000 0.0425      0      0 9 150      0
19      5 1939.500 60.0000 30.0425 10.0000      0      0 9 150      0
20      5 1949.500 70.0000 40.0425 6.8442      0      0 9 150      0
21      6 1934.246 44.3314 23.0437 1.9563      0      2 10 163      2
3150      6 1936.203 46.2877 25.0000 3.7123      2      2 10 163      2
3151      6 1939.915 50.0000 28.7123 1.2877      2      2 10 163      2
3152      6 1941.203 51.2877 30.0000 8.7123      2      2 10 163      2
3153      6 1949.915 60.0000 38.7123 2.5413      2      1 10 163      2
      dob age1st  agein  ageout
3142 1886.340 24.7206 47.9067 69.6794
3143 1886.340 24.7206 47.9067 69.6794
3144 1886.340 24.7206 47.9067 69.6794
3145 1886.340 24.7206 47.9067 69.6794
17 1879.500 29.9575 54.7465 76.8442
18 1879.500 29.9575 54.7465 76.8442
19 1879.500 29.9575 54.7465 76.8442
20 1879.500 29.9575 54.7465 76.8442
21 1889.915 21.2877 44.3314 62.5413
3150 1889.915 21.2877 44.3314 62.5413

```

```
3151 1889.915 21.2877 44.3314 62.5413
3152 1889.915 21.2877 44.3314 62.5413
3153 1889.915 21.2877 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 )
```

	per	age	tfh	lex.dur	lex.Cst	lex.Xst	lex.id	id	icd	exposure
4	1934.246	47.9067	23.1861	21.7727	0	1	4	8	527	9
5	1934.246	54.7465	24.7890	22.0977	0	1	5	9	150	0
6	1934.246	44.3314	23.0437	18.2099	0	2	6	10	163	2
	dob	age1st	agein	ageout						
4	1886.340	24.7206	47.9067	69.6794						
5	1879.500	29.9575	54.7465	76.8442						
6	1889.915	21.2877	44.3314	62.5413						

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:	
	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 )
```

	per	age	tfh	lex.dur	lex.Cst	lex.Xst	lex.id	id	icd	exposure
683	1934.246	47.9067	23.1861	21.7727	HiExp	D.oth	4	8	527	9
5	1934.246	54.7465	24.7890	22.0977	Alive	D.oth	5	9	150	0
6	1934.246	44.3314	23.0437	1.9563	Alive	HiExp	6	10	163	2
685	1936.203	46.2877	25.0000	16.2536	HiExp	D.lung	6	10	163	2
	dob	age1st	agein	ageout	agehi					
683	1886.340	24.7206	47.9067	69.6794	30.27616					
5	1879.500	29.9575	54.7465	76.8442	Inf					
6	1889.915	21.2877	44.3314	62.5413	46.28770					
685	1889.915	21.2877	44.3314	62.5413	46.28770					

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

Transitions:

	To							
From	Alive	HiExp	D.oth	D.lung	Records:	Events:	Risk time:	Persons:
	39	83	279	65	466	427	10.77	466
	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
683	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
685	1936.203	46.2877	25.0000	0.00000	16.2536	Hi	D.lung(Hi)	6	10	163
	exposure	dob	age1st	agein	ageout	agehi				
683	9	1886.340	24.7206	47.9067	69.6794	30.27616				
5	0	1879.500	29.9575	54.7465	76.8442	Inf				
6	2	1889.915	21.2877	44.3314	62.5413	46.28770				
685	2	1889.915	21.2877	44.3314	62.5413	46.28770				

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

Transitions:

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

Transitions:

	To								
From	Risk time:	Persons:							

Alive	10.77	466
Hi	4.58	296
Sum	15.35	679

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.