Time dependent covariates in Lexis objects

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Bendix Carstensen Steno Diabetes Center Copenhagen, Herley, Denmark & Department of Biostatistics, University of Copenhagen

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Chapter 1

Overview and rationale

This note describes the functions addCov.Lexis, designed to add values of clinical measurements, and addDrug.Lexis designed to add drug exposure to time-split Lexis objects.

If time-dependent variables are binary, such as for example "occurrence of CVD diagnosis" it may be relevant to define a new state as, say, CVD; this is the business of the funtions cutlexis and its cousins. The purposes of the two functions discussed here are to append quantitative variables that in principle can take any value.

Both functions are so-called S3 methods for Lexis objects, so in code you can omit the ".Lexis". Note that neither cutLexis, splitLexis or splitMulti are S3 methods (there is no "." in the names).

1.1 addCov.Lexis

...provides the ability to amend a Lexis object with clinical measurements taken at different times, and propagate the values as LOCF (Last Observation Carried Forward) to all subsequent records. This means that time-splitting of a Lexis object after adding clinical measurements will be meaningful, because both splitLexis and splitMulti will carry variables forward across the split records. The follow-up in the resulting Lexis object will be cut at dates of clinical measurement.

addCov.Lexis will also propagate missing values supplied as measurements. Therefore, if you want to have LOCF across supplied times of measurement you must explicitly apply tidyr::fill to the resulting Lexis object, after a suitable group_by.

1.2 addDrug.Lexis

As opposed to this, addDrug.Lexis will first use drug information at each date of recorded drug purchase, and subsequently compute cumulative exposure measures at the times in the resulting Lexis object. This is essentially by linear interpolation, so it will not be meaningful to further split an object resulting from addDrug.Lexis—LOCF is not meaningful for continuously time-varying covariates such as cumulative exposure.

If persons have very frequent drug purchases, the intervals may become very small and the sheer number of records may present an impediment to analysis. Therefore the function coarse. Lexis is provided to collapse adjacent follow-up records. Note that

coarse.Lexis is not an S3 method.

Chapter 2

addCov.Lexis

2.1 Rationale

The function has arisen out of a need to attach values measured at clinical visits to a Lexis object representing follow-up for events constituting a multistate model. Hence the data frame with measurements at clinical visits will be called clin for mnemonic reasons.

2.2 Example

For illustration we devise a small bogus cohort of 3 people, where we convert the character dates into numerical variables (fractional years) using cal.yr. Note that we are using a character variable as id:

```
> xcoh <- structure(list(id = c("A", "B", "C"),
                      \label{eq:birth} \mbox{birth} \; = \; c \, ("1952-07-14", \; "1954-04-01", \; "1987-06-10") \, ,
                      entry = c("1965-08-04", "1972-09-08", "1991-12-23"),
+
                       exit = c("1997-06-27", "1995-05-23", "1998-07-24").
                       fail = c(1, 0, 1)),
                  .Names = c("id", "birth", "entry", "exit", "fail"), row.names = c("1", "2", "3"),
                      class = "data.frame" )
> xcoh$dob <- cal.yr(xcoh$birth)</pre>
> xcoh$doe <- cal.yr(xcoh$entry)
> xcoh$dox <- cal.yr(xcoh$exit )</pre>
> xcoh
                                                 dob
 id
          birth
                     entry
                                 exit fail
                                                          doe
1 A 1952-07-14 1965-08-04 1997-06-27 1 1952.533 1965.589 1997.485
2 B 1954-04-01 1972-09-08 1995-05-23
                                       0 1954.246 1972.686 1995.388
```

2.2.1 A Lexis object

Define this as a Lexis object with timescales calendar time (per, period) and age (age):

addCov.Lexis 2.2 Example 5

```
exit.status = factor(fail, 0:1, c("Alive", "Dead")),
               data = xcoh)
NOTE: entry.status has been set to "Alive" for all.
> str(Lcoh)
Classes 'Lexis' and 'data.frame':
                                        3 obs. of 14 variables:
 $ per : 'cal.yr' num 1966 1973 1992
       : 'cal.yr' num 13.06 18.44 4.54
 $ lex.dur: 'cal.yr' num 31.9 22.7 6.58
 $ lex.Cst: Factor w/ 2 levels "Alive", "Dead": 1 1 1
 $ lex.Xst: Factor w/ 2 levels "Alive", "Dead": 2 1 2
 $ lex.id : chr "A" "B" "C"
                "A" "B" "C"
         : chr
 $ id
                "1952-07-14" "1954-04-01" "1987-06-10"
 $ birth : chr
 $ entry : chr "1965-08-04" "1972-09-08" "1991-12-23"
         : chr "1997-06-27" "1995-05-23" "1998-07-24"
 $ exit
 $ fail
        : num 1 0 1
         : 'cal.yr' num 1953 1954 1987
         : 'cal.yr' num 1966 1973 1992
 $ doe
         : 'cal.yr' num 1997 1995 1999
 - attr(*, "time.scales")= chr [1:2] "per" "age"
 - attr(*, "time.since") = chr [1:2] "" ""
 - attr(*, "breaks")=List of 2
  ..$ per: NULL
  ..$ age: NULL
> (Lx <- Lcoh[,1:6])
           per
 lex.id
                 age lex.dur lex.Cst lex.Xst
     A 1965.59 13.06 31.90
                               Alive
                                        Dead
     B 1972.69 18.44 22.70
                               Alive
                                       Alive
     C 1991.97 4.54
                        6.58
                               Alive
                                        Dead
```

Factor or character lex.id?

Note that when the id argument to Lexis is a character variable then the lex.id will be a factor. Which, if each person has a lot of records may save time, but if you subset may be a waste of space. Moreover merging (i.e. joining in the language of tidyverse) may present problems with different levels. merge from the base R, will coerce to factor with union of levels as levels, where as the _join functions from dplyr will coerce to character.

Thus the most reasonable strategy thus seems to keep lex.id as a character variable.

6 2.2 Example addLex

```
> Lx
lex.id
                  age lex.dur lex.Cst lex.Xst
            per
      A 1965.59 13.06
                         31.90
                                 Alive
                                           Dead
      B 1972.69 18.44
                         22.70
                                 Alive
                                          Alive
      C 1991.97 4.54
                          6.58
                                 Alive
                                           Dead
```

Clinical measurements

Then we generate data frame with clinical examination data, that is date of examination in per, some (bogus) clinical measurements and also names of the examination rounds:

```
> clin <- data.frame(lex.id = c("A", "A", "C", "B",
                                                      "C").
                         per = cal.yr(c("1977-3-17"
                                         "1973-7-29"
+
                                         "1996-3-1",
                                         "1990-7-14"
+
                                         "1989-1-31")),
                          bp = c(120, 140, 160, 157, 145),
                        chol = c(NA, 5, 8, 9, 6),
                        xnam = c("X2", "X1", "X1", "X2", "X0"),
           stringsAsFactors = FALSE)
> str(clin)
'data.frame':
                     5 obs. of 5 variables:
               "A" "A" "C" "B" ...
 $ lex.id: chr
         : 'cal.yr' num 1977 1974 1996 1991 1989
               120 140 160 157 145
 $ bp
         : num
 $ chol
        : num
                NA 5 8 9 6
                "X2" "X1" "X1" "X2" ...
 $ xnam : chr
> clin
  lex.id
              per bp chol xnam
1
       A 1977.206 120
                         NA
       A 1973.573 140
                          5
                              X 1
3
       C 1996.163 160
                          8
                              X 1
4
                              X2
       B 1990.531 157
                          9
5
       C 1989.083 145
                              XΟ
```

We set up this data frame with an id variable called lex.id and a date of examination, per, that has the same name as one of the time scales in the Lexis object Lx. Note that we have chosen a measurement for person C from 1989—before the person's entry to the study, and have an NA for chol for person A.

2.2.2 Adding clinical data

There is a slightly different behaviour according to whether the variable with the name of the examination is given or not, and whether the name of the (incomplete) time scale is given or not:

```
> (Cx <- addCov.Lexis(Lx, clin))
            per
                   age
                       tfc lex.dur lex.Cst lex.Xst exnam
                                                             bp chol xnam
      A 1965.59 13.06
                               7.98
                                                                   NA <NA>
                         NA
                                       Alive
                                               Alive
                                                       < NA >
                                                             NA
      A 1973.57 21.04 0.00
                               3.63
                                                        ex1 140
                                                                   5
                                                                        X1
                                       Alive
                                               Alive
      A 1977.21 24.67 0.00
                              20.28
                                       Alive
                                                Dead
                                                        ex2 120
                                                                   NA
                                                                        Х2
      B 1972.69 18.44
                              17.85
                                       Alive
                                                                   NA <NA>
                                               Alive
                                                      < NA >
```

```
B 1990.53 36.28 0.00
                          4.86
                                  Alive
                                          Alive
                                                   ex1 157
                                                               9
                                                                   X2
C 1991.97
           4.54 2.89
                          4.19
                                                   ex1 145
                                                               6
                                                                   XΟ
                                 Alive
                                          Alive
C 1996.16
           8.73 0.00
                          2.40
                                 Alive
                                           Dead
                                                   ex2 160
                                                                   X1
```

Note that the clinical measurement preceding the entry of person C is included, and that the tfc (time from clinical measurement) is correctly rendered, we a non-zero value at date of entry.

We also see that a variable exnam is constructed with consecutive numbering of examinations within each person, while the variable xnam is just carried over as any other.

If we explicitly give the name of the variable holding the examination names we do not get a constructed exnam. We can also define the name of the (incomplete) timescale to hold the time since measurement, in this case as tfCl:

```
> (Dx <- addCov.Lexis(Lx, clin, exnam = "xnam", tfc = "tfCl"))
                   age tfCl lex.dur lex.Cst lex.Xst xnam
 lex.id
            per
      A 1965.59 13.06
                         NA
                               7.98
                                       Alive
                                               Alive <NA>
                                                            NA
                                                                  NA
      A 1973.57 21.04 0.00
                               3.63
                                       Alive
                                               Alive
                                                        X1 140
                                                                  5
      A 1977.21 24.67 0.00
                              20.28
                                       Alive
                                                Dead
                                                        X2 120
                                                                 NA
      B 1972.69 18.44
                              17.85
                         NA
                                       Alive
                                               Alive <NA>
                                                            NΑ
                                                                 NA
      B 1990.53 36.28 0.00
                               4.86
                                                                  9
                                       Alive
                                               Alive
                                                        X2 157
                 4.54 2.89
                                                                  6
      C 1991.97
                                4.19
                                       Alive
                                                Alive
                                                        XO 145
      C 1996.16 8.73 0.00
                                2.40
                                       Alive
                                                Dead
                                                        X1 160
                                                                  8
> summary(Dx, t=T)
Transitions:
     Tο
        Alive Dead
                     Records:
                               Events: Risk time:
From
                                                     Persons:
  Alive
            5
                  2
                            7
                                      2
                                             61.18
                                                            3
Timescales:
 per age tfCl
       "" "Х"
```

2.3 Exchanging split and add

As noted in the beginning of this note, addCov.Lexis uses LOCF, and so it is commutative with splitLexis:

```
> # split BEFORE add
> Lb <- addCov.Lexis(splitLexis(Lx,
                         time.scale = "age",
                             breaks = seq(0, 80, 5)),
+
                      clin,
                      exnam = "xnam" )
> Lb
                         tfc lex.dur lex.Cst lex.Xst xnam bp chol
lex.id
            per
                   age
      A 1965.59 13.06
                          NA
                                1.94
                                        Alive
                                                Alive <NA>
      A 1967.53 15.00
                          NA
                                5.00
                                        Alive
                                                Alive <NA>
                                                                  NA
      A 1972.53 20.00
                          NA
                                1.04
                                        Alive
                                                Alive <NA>
                                                             NA
                                                                  NA
      A 1973.57 21.04
                        0.00
                                3.63
                                                         X1 140
                                        Alive
                                                Alive
                                                                   5
      A 1977.21 24.67
                        0.00
                                0.33
                                                         X2 120
                                        Alive
                                                Alive
                                                                  NA
      A 1977.53 25.00
                        0.33
                                5.00
                                        Alive
                                                Alive
                                                         X2 120
                                                                  NA
      A 1982.53 30.00 5.33
                                5.00
                                        Alive
                                                Alive
                                                         X2 120
```

```
A 1987.53 35.00 10.33
                               5.00
                                      Alive
                                              Alive
                                                      X2 120
                                                                NA
      A 1992.53 40.00 15.33
                               4.95
                                      Alive
                                               Dead
                                                      X2 120
                                                                NA
     B 1972.69 18.44
                         NA
                               1.56
                                      Alive
                                              Alive <NA>
                                                          NA
                                                                NA
     B 1974.25 20.00
                         NA
                               5.00
                                      Alive
                                              Alive <NA>
                                                          NA
     B 1979.25 25.00
                               5.00
                                      Alive
                                              Alive <NA>
                         NA
                                                          NA
     B 1984.25 30.00
                               5.00
                         NA
                                      Alive
                                              Alive <NA>
                                                          NA
     B 1989.25 35.00
                         NA
                               1.28
                                     Alive
                                              Alive <NA>
                                                          NA
     B 1990.53 36.28
                      0.00
                               3.72
                                     Alive
                                              Alive
                                                       X2 157
     B 1994.25 40.00
                       3.72
                               1.14
                                    Alive
                                              Alive
                                                      X2 157
                                                                 9
     C 1991.97
                 4.54
                       2.89
                               0.46
                                    Alive
                                              Alive
                                                      XO 145
                                                                 6
     C 1992.44
                5.00
                      3.35
                               3.73
                                      Alive
                                              Alive
                                                       XO 145
                                                                 6
                               1.27
     C 1996.16
                8.73
                      0.00
                                                      X1 160
                                                                 8
                                      Alive
                                              Alive
     C 1997.44 10.00
                      1.27
                               1.12
                                      Alive
                                               Dead
                                                      X1 160
> # split AFTER add
> La <- splitLexis(addCov.Lexis(Lx,
                             exnam = "xnam"),
                   time.scale = "age",
                       breaks = seq(0, 80, 5))
> La
                        tfc lex.dur lex.Cst lex.Xst xnam
lex.id
                  age
                                                          bp chol
            per
      A 1965.59 13.06
                             1.94
                                              Alive <NA>
                         NA
                                     Alive
                                                          NA
      A 1967.53 15.00
                               5.00
                                      Alive
                                              Alive <NA>
                         NA
                                                          NA
                                                                NA
      A 1972.53 20.00
                         NA
                               1.04
                                      Alive
                                              Alive <NA>
                                                          NA
      A 1973.57 21.04
                      0.00
                               3.63
                                     Alive
                                              Alive
                                                      X1 140
                                                                5
      A 1977.21 24.67
                       0.00
                               0.33
                                     Alive
                                              Alive
                                                      X2 120
                                                                NA
     A 1977.53 25.00
                                                      X2 120
                      0.33
                               5.00
                                     Alive
                                              Alive
                                                                NA
     A 1982.53 30.00
                      5.33
                               5.00
                                     Alive
                                              Alive
                                                      X2 120
      A 1987.53 35.00 10.33
                               5.00 Alive
                                              Alive
                                                      X2 120
      A 1992.53 40.00 15.33
                               4.95
                                     Alive
                                               Dead
                                                      X2 120
     B 1972.69 18.44
                               1.56
                                     Alive
                                              Alive <NA>
                         NA
                                                          NA
     B 1974.25 20.00
                                              Alive <NA>
                         NA
                               5.00
                                     Alive
                                                          NA
                                                                NA
     B 1979.25 25.00
                               5.00
                                     Alive
                                              Alive <NA>
                         NA
                                                          NA
                                                                NA
     B 1984.25 30.00
                         NA
                               5.00
                                     Alive
                                              Alive <NA>
                                                          NA
     B 1989.25 35.00
                                              Alive <NA>
                         NA
                               1.28
                                     Alive
                                                          NA
                                                                NA
     B 1990.53 36.28
                      0.00
                               3.72
                                     Alive
                                              Alive
                                                      X2 157
                                                                9
     B 1994.25 40.00
                      3.72
                               1.14
                                     Alive
                                              Alive
                                                       X2 157
                                                                 9
                                                                 6
     C 1991.97
                4.54
                      2.89
                               0.46
                                      Alive
                                              Alive
                                                      XO 145
     C 1992.44
                5.00
                      3.35
                               3.73
                                      Alive
                                              Alive
                                                       XO 145
                                                                 6
     C 1996.16 8.73 0.00
                               1.27
                                                                 8
                                      Alive
                                              Alive
                                                       X1 160
      C 1997.44 10.00
                      1.27
                               1.12
                                      Alive
                                                      X1 160
                                                                 8
                                               Dead
```

We see that the results are identical, bar the sequence of variables and attributes.

We can more explicitly verify that the resulting data frames are the same:

addCov.Lexis 2.4 Filling the NAs 9

The same goes for splitMulti:

```
> ## split BEFORE add
> Mb <- addCov.Lexis(splitMulti(Lx, age = seq(0, 80, 5)),
                      clin,
+
                      exnam = "xnam" )
>
 ##
> ## split AFTER add
> Ma <- splitMulti(addCov.Lexis(Lx,
                                 clin,
                                 exnam = "xnam"),
                    age = seq(0, 80, 5))
> La$tfc == Mb$tfc
 [1]
       NA
            NA
                 NA TRUE TRUE TRUE TRUE TRUE TRUE
                                                      NA
                                                           NA
                                                                 NA
                                                                      NA
                                                                           NA TRUE TRUE TRUE
[18] TRUE TRUE TRUE
> Ma$tfc == Mb$tfc
 [1]
       NA
            NA
                 NA TRUE TRUE TRUE TRUE TRUE TRUE
                                                      NA
                                                           NA
                                                                 NA
                                                                      NA
                                                                           NA TRUE TRUE TRUE
[18] TRUE TRUE TRUE
```

In summary, because both addCov.Lexis and splitLexis/splitMulti use LOCF for covariates the order of splitting and adding does not matter.

This is certainly not the case with addDrug.Lexis as we shall see.

2.4 Filling the NAs

As mentioned in the beginning, clinical measurements given as NA in the clin data frame are carried forward. If you want to have these replaced by 'older' clinical measurements you can do that explicitly by dplyr::fill with a construction like:

```
> cov <- c("bp", "chol")
> Lx <- La
> Lx <- group_by(Lx, lex.id) %>%
+ fill(all_of(cov)) %>%
+ ungroup()
> class(Lx)
[1] "tbl_df" "tbl" "data.frame"
```

We see that the Lexis attributes are lost by using the group_by function, so we fish out the covariates from the tibble and stick them back into the Lexis object:

```
> Lx[,cov] <- as.data.frame(group_by(Lx, lex.id)
                             %>% fill(all_of(cov)))[,cov]
> class(Lx)
[1] "Lexis"
                 "data.frame"
> La
lex.id
                         tfc lex.dur lex.Cst lex.Xst xnam
            per
                  age
      A 1965.59 13.06
                                1.94
                                       Alive
                                                Alive <NA>
                          NA
      A 1967.53 15.00
                          NA
                                5.00
                                       Alive
                                                Alive <NA>
                                                            NA
                                                                  NA
                                1.04
                                                Alive <NA>
      A 1972.53 20.00
                          NA
                                       Alive
                                                            NA
                                                                  NA
      A 1973.57 21.04
                       0.00
                                3.63
                                                        X1 140
                                                                  5
                                       Alive
                                                Alive
      A 1977.21 24.67
                       0.00
                                0.33
                                       Alive
                                                Alive
                                                        X2 120
                                                                  NA
      A 1977.53 25.00 0.33
                                5.00
                                       Alive
                                                Alive
                                                        X2 120
```

	1982.53			5.00	Alive	Alive	Х2	120	NA
Α	1987.53	35.00	10.33	5.00	Alive	Alive	Х2	120	NA
Α	1992.53	40.00	15.33	4.95	Alive	Dead	Х2	120	NA
В	1972.69	18.44	NA	1.56	Alive	Alive	<NA $>$	NA	NA
В	1974.25	20.00	NA	5.00	Alive	Alive	<NA $>$	NA	NA
В	1979.25	25.00	NA	5.00	Alive	Alive	<NA $>$	NA	NA
В	1984.25	30.00	NA	5.00	Alive	Alive	<NA $>$	NA	NA
В	1989.25	35.00	NA	1.28	Alive	Alive	<NA $>$	NA	NA
В	1990.53	36.28	0.00	3.72	Alive	Alive	Х2	157	9
В	1994.25	40.00	3.72	1.14	Alive	Alive	Х2	157	9
C	1991.97	4.54	2.89	0.46	Alive	Alive	ΧO	145	
C	1992.44	5.00	3.35	3.73	Alive	Alive	ΧO	145	
C	1996.16	8.73	0.00	1.27	Alive	Alive	X1	160	
C	1997.44	10.00	1.27	1.12	Alive	Dead	X1	160	8
> Lx									
lex.id	per	age	tfc	lex.dur	lex.Cst	lex.Xst	xnam	bр	chol
A	1965.59	13.06	NA	1.94	Alive	Alive	<na></na>	ΝĀ	NA
	1967.53			5.00	Alive	Alive	<NA $>$	NA	NA
Α	1972.53	20.00	NA	1.04	Alive	Alive	<na></na>	NA	NA
Α	1973.57	21.04	0.00	3.63	Alive	Alive	X1	140	5
Α	1977.21	24.67	0.00	0.33	Alive	Alive	Х2	120	
Α	1977.53	25.00	0.33	5.00	Alive	Alive	Х2	120	5
Α	1982.53	30.00	5.33	5.00	Alive	Alive	Х2	120	5
Α	1987.53	35.00	10.33	5.00	Alive	Alive	Х2	120	5
Α	1992.53	40.00	15.33	4.95	Alive	Dead	Х2	120	5
В	1972.69	18.44	NA	1.56	Alive	Alive	<NA $>$	NA	NA
В	1974.25	20.00	NA	5.00	Alive	Alive	<NA $>$	NA	NA
В	1979.25	25.00	NA	5.00	Alive	Alive	< NA >	NA	NA
В	1984.25	30.00	NA	5.00	Alive	Alive	<NA $>$	NA	NA
В	1989.25	35.00	NA	1.28	Alive	Alive	<NA $>$	NA	NA
В	1990.53	36.28	0.00	3.72	Alive	Alive	Х2	157	9
В	1994.25	40.00	3.72	1.14	Alive	Alive	Х2	157	
	1991.97					Alive	XO	145	
	1992.44			3.73		Alive	ΧO	145	
C	1996.16	8.73	0.00	1.27	Alive	Alive	X1	160	
~	1997.44		1.27	1.12		Dead	X1		8

The slightly convoluted code where the covariate columns are explicitly selected, owes to the fact that the dplyr functions will strip the data frames of the Lexis attributes. So we needed to use fill to just generate the covariates and not touch the Lexis object itself.

This should of course be built into addCov.Lexis as a separate argument, but is not yet. Note that the tfc, time from clinical measurement, is now not a valid time scale variable any more; the 5 in chol is measured at 1973.7 but tfc is reset to 0 at 1977.21, even if only bp but not chol is measured at that time. If you want that remedied you will have to use addCov.Lexis twice, one with a clin data frame with only bp and another with a data frame with only chol, each generating a differently named variable holding the time from clinical measurement.

This is a problem that comes from the structure of the supplied *data* not from the program features; in the example we had basically measurements of different clinical variables at different times, and so necessarily also a need for different times since last measurement.

Chapter 3

addDrug.Lexis

The general purpose of the function is to amend a Lexis object with drug exposure data. The data base with information on a specific drug is assumed to be a data frame with one entry per drug purchase (or prescription), containing the date and the amount purchased and optionally the prescribed dosage (that is how much is supposed to be taken per time). We assume that we have such a data base for each drug of interest, which also includes an id variable, lex.id, that matches the lex.id variable in the Lexis object.

For each type of drug the function derives 4 variables:

```
ex : logical, is the person currently exposed
tf : numeric, time since first purchase
ct : numeric, cumulative time on the drug
cd : numeric, cumulative dose of the drug
```

These names are pre- or suf-fixed by the drug name, so that exposures to different drugs can be distinguished; see the examples.

The resulting Lexis object has extra records corresponding to cuts at each drug purchase and at each expiry date of a purchase. For each purchase the coverage period is derived (different methods for this are available), and if the end of this (the expiry date) is earlier than the next purchase of the person, the person is considered off the drug from the expiry date, and a cut in the follow-up is generated with ex set to FALSE.

3.1 The help example

The following is a slight modification of the code from the example section of the help page for addDrug.Lexis

First we generate follow-up of 2 persons, and split the follow-up in intervals of length 0.6 years along the calendar time scale, per:

```
> fu <- data.frame(doe = c(2006, 2008), \\ + dox = c(2015, 2018), \\ + dob = c(1950, 1951), \\ + xst = factor(c("A", "D"))) \\ > Lx <- Lexis(entry = list(per = doe, \\ + age = doe- dob), \\ + exit = list(per = dox), \\ + exit.status = xst, \\ + data = fu)
```

```
NOTE: entry.status has been set to "A" for all.
> Lx <- subset(Lx, select = -c(doe, dob, dox, xst))
> Sx \leftarrow splitLexis(Lx, "per", breaks = seg(1990, 2020, 0.6))
> summary(Sx)
Transitions:
    То
From A D Records: Events: Risk time: Persons:
   A 32 1
                33
                               19
                        1
> str(Sx)
Classes 'Lexis' and 'data.frame':
                                         33 obs. of 6 variables:
 $ lex.id : int 1 1 1 1 1 1 1 1 1 ...
       : num 2006 2006 2007 2007 2008 ...
          : num 56 56.2 56.8 57.4 58 ...
 $ lex.dur: num 0.2 0.6 0.6 0.6 0.6 ...
 $ lex.Cst: Factor w/ 2 levels "A", "D": 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Xst: Factor w/ 2 levels "A","D": 1 1 1 1 1 1 1 1 1 1 1 ...
 - attr(*, "breaks")=List of 2
  ..$ per: num [1:51] 1990 1991 1991 1992 1992 ...
  ..$ age: NULL
 - attr(*, "time.scales")= chr [1:2] "per" "age"
 - attr(*, "time.since")= chr [1:2] "" ""
```

Note that as opposed to the previous example, the time scales are not of class cal.yr, they are just numerical.

Then we generate example drug purchases for these two persons, one data frame for each of the drugs F and G. Note that we generate $lex.id \in (1,2)$ referring to the values of lex.id in the lexis object Sx.

We do not need to sort the drug purchase data frames (it is done internally by addDrug.Lexis), but it makes it easier to grasp the structure. Note that we generated the drug purchase files with the required variable names.

The way purchase data is supplied to the function is in a list where each element is a data frame of purchase records for one type of drug. The list must be named, because the names are used as prefixes of the generated exposure variables. We can show the resulting data in a list:

```
2005.311
6
   2007.595
              3
                      2
                      2
7
   2011.710
              4
8
  2011.812
              3
                      2
9 2012.865
              2
                      2
                      2
              2
10 2013.331
                      2
11 2013.417
                      2
12 2013.932
$G
        per amt lex.id
   2009.630 1.3
1
                      1
2
   2012.987 1.3
                      1
3
  2013.018 1.3
                      1
4
  2016.954 0.7
5 2017.924 1.0
6 2009.089 1.3
7 2011.599 0.7
8 2014.566 1.0
9 2016.912 0.7
                      2
10 2017.004 1.0
> Lx
 lex.id per age lex.dur lex.Cst lex.Xst
      1 2006
             56
                       9
                                Α
      2 2008 57
                       10
                                Α
                                        D
```

Note that we have generated data so that there are drug purchases of drug F that is before start of follow-up for person 2.

We can then expand the time-split Lexis object, Sx with the drug information. addDrug.Lexis not only adds 8 variables (4 from each drug), it also adds records representing cuts at the purchase dates and possible expiry dates.

```
> summary(Sx) ; names(Sx)
Transitions:
     То
From A D Records:
                     Events: Risk time:
                                         Persons:
   A 32 1
                 33
                           1
                        "age"
[1] "lex.id" "per"
                                  "lex.dur" "lex.Cst" "lex.Xst"
> ex1 <- addDrug.Lexis(Sx, pdat, method = "ext") # default
NOTE: timescale taken as 'per'
NOTE: end of exposure based on differences in purchase times (per)
 and amount purchased (amt).
> summary(ex1) ; names(ex1)
Transitions:
     Τо
From A D Records:
                     Events: Risk time:
                                         Persons:
                           1
                                     19
              "per"
                                   "lex.dur" "lex.Cst" "lex.Xst" "F.ex"
 [1] "lex.id"
                         "age"
                                                                            "F.tf"
 [9] "F.ct"
               "F.cd"
                         "G.ex"
                                   "G.tf"
                                            "G.ct"
> print(ex1, nd = 2)
```

low id non	200	lex.dur	low Cat	low Vat	E 037	E +f	E o+	E ad	C 037	C +f	C at	Cod
lex.id per 1 2006.00		0.20	Tex.CSt		FALSE				G.ex FALSE			
1 2006.20		0.60	A		FALSE				FALSE			
1 2006.20		0.60	A A		FALSE				FALSE			
1 2007.40					FALSE				FALSE			
		0.60	A									
1 2008.00		0.60	A		FALSE				FALSE			
1 2008.60		0.60	A		FALSE				FALSE			
1 2009.20		0.43	A		FALSE				FALSE			
1 2009.63		0.17	A		FALSE			0.00		0.00		
1 2009.80		0.60	A		FALSE			0.00		0.17		
1 2010.40		0.60	A		FALSE			0.00		0.77		
1 2011.00		0.60	A		FALSE			0.00		1.37		
1 2011.60		0.60	A		FALSE			0.00		1.97		
1 2012.20		0.60	A		FALSE			0.00		2.57		
1 2012.80		0.19	A		FALSE			0.00		3.17		
1 2012.99		0.03	A		FALSE			0.00		3.36		
1 2013.02		0.03	A		FALSE			0.00		3.39		
1 2013.05		0.35	A		FALSE				FALSE			
1 2013.40		0.56	A	A	FALSE				FALSE			
1 2013.96		0.00	A	A			0.00		FALSE			
1 2013.96		0.04	A	A			0.00		FALSE			
1 2014.00		0.25	A	A			0.04		FALSE			
1 2014.25		0.00	A	A			0.29		FALSE			
1 2014.25		0.26	A	A			0.29		FALSE			
1 2014.51		0.00	A	A	TRUE	0.54	0.54		FALSE			
1 2014.51		0.09	A	Α			0.54		FALSE			
1 2014.60	64.60	0.10	A	Α	TRUE	0.64	0.64	9.41	FALSE	4.97	3.42	3.90
1 2014.70	64.70	0.00	Α	A	FALSE	0.74	0.74	11.00	FALSE	5.07	3.42	3.90
1 2014.70	64.70	0.29	Α	A	FALSE	0.74	0.74	11.00	FALSE	5.07	3.42	3.90
1 2014.99	64.99	0.01	A	A	TRUE	1.03	0.74	11.00	FALSE	5.36	3.42	3.90
2 2008.00	57.00	0.60	A	A	TRUE	0.00	0.40	0.35	FALSE	0.00	0.00	0.00
2 2008.60	57.60	0.49	A	A	TRUE	0.60	1.00	0.88	FALSE	0.00	0.00	0.00
2 2009.09	58.09	0.11	A	A	TRUE	1.09	1.49	1.31	TRUE	0.00	0.00	0.00
2 2009.20	58.20	0.60	A	A	TRUE	1.20	1.60	1.40	TRUE	0.11	0.11	0.06
2 2009.80	58.80	0.60	A	Α	TRUE	1.80	2.20	1.93	TRUE	0.71	0.71	0.37
2 2010.40	59.40	0.60	A	A	TRUE	2.40	2.80	2.46	TRUE	1.31	1.31	0.68
2 2011.00	60.00	0.02	Α	Α	TRUE	3.00	3.40	2.98	TRUE	1.91	1.91	0.99
2 2011.02	60.02	0.00	Α	Α	FALSE	3.02	3.43	3.00	TRUE	1.93	1.93	1.00
2 2011.02	60.02	0.58	A	Α	FALSE	3.02	3.43	3.00	TRUE	1.93	1.93	1.00
2 2011.60	60.60	0.00	Α	Α	FALSE	3.60	3.43	3.00	TRUE	2.51	2.51	1.30
2 2011.60	60.60	0.11	Α	Α	FALSE	3.60	3.43	3.00	TRUE	2.51	2.51	1.30
2 2011.71	60.71	0.00	Α	Α	TRUE	3.71	3.43	3.00	TRUE	2.62	2.62	1.36
2 2011.71	60.71	0.10	Α	Α	TRUE	3.71	3.43	3.00	TRUE	2.62	2.62	1.36
2 2011.81	60.81	0.08	A	Α	TRUE	3.81	3.53	7.00	TRUE	2.72	2.72	1.41
2 2011.89	60.89	0.31	Α	A	FALSE	3.89	3.61	10.00	TRUE	2.80	2.80	1.45
2 2012.20	61.20	0.60	A	A	FALSE	4.20	3.61	10.00	TRUE	3.11	3.11	1.61
2 2012.80	61.80	0.07	A	A	FALSE	4.80	3.61	10.00	TRUE	3.71	3.71	1.92
2 2012.87	61.87	0.09	A	A	TRUE	4.87	3.61	10.00	TRUE	3.78	3.78	1.96
2 2012.95		0.38	Α	A					FALSE			
2 2013.33		0.07	A	Α					FALSE			
2 2013.40		0.02	A	Α					FALSE			
2 2013.42		0.09	A	Α					FALSE			
2 2013.50		0.43	Α	Α	FALSE							
2 2013.93		0.07	Α	Α					FALSE			
2 2014.00		0.45	A	A					FALSE			
2 2014.45		0.12	A		FALSE							
2 2014.57		0.03	A		FALSE							
		_			_		_	-	_	-	_	

```
2 2014.60 63.60
                        0.60
                                  Α
                                           A FALSE 6.60 4.76 18.00
                                                                    TRUE 5.51 3.90 2.01
      2 2015.20 64.20
                        0.60
                                           A FALSE 7.20 4.76 18.00
                                                                    TRUE 6.11 4.50 2.27
                                   Α
      2 2015.80 64.80
                        0.60
                                   Α
                                           A FALSE 7.80 4.76 18.00
                                                                    TRUE 6.71 5.10 2.53
      2 2016.40 65.40
                        0.51
                                   Α
                                           A FALSE 8.40 4.76 18.00
                                                                    TRUE 7.31 5.70 2.78
      2 2016.91 65.91
                        0.09
                                   Α
                                           A FALSE 8.91 4.76 18.00
                                                                    TRUE 7.82 6.21 3.00
      2 2017.00 66.00
                        0.00
                                           A FALSE 9.00 4.76 18.00
                                                                    TRUE 7.91 6.30 3.67
                                   Α
      2 2017.00 66.00
                        0.13
                                           A FALSE 9.00 4.76 18.00
                                                                    TRUE 7.91 6.30 3.70
                                   Α
      2 2017.14 66.14
                        0.46
                                   Α
                                           A FALSE 9.14 4.76 18.00 FALSE 8.05 6.43 4.70
      2 2017.60 66.60
                        0.40
                                   Α
                                           D FALSE 9.60 4.76 18.00 FALSE 8.51 6.43 4.70
> ex2 <- addDrug.Lexis(Sx, pdat, method = "ext", grace = 0.5)
NOTE: timescale taken as 'per'
Values of grace has been recycled across 2 drugs
NOTE: end of exposure based on differences in purchase times (per)
 and amount purchased (amt).
> summary(ex2)
Transitions:
    То
From A D Records: Events: Risk time: Persons:
                63
                         1
> print(ex2, nd = 2)
                 age lex.dur lex.Cst lex.Xst F.ex F.tf F.ct F.cd G.ex G.tf G.ct G.cd
 lex.id
           per
      1 2006.00 56.00
                        0.20
                                           A FALSE 0.00 0.00
                                                              0.00 FALSE 0.00 0.00 0.00
                                   Α
                                                              0.00 FALSE 0.00 0.00 0.00
      1 2006.20 56.20
                        0.60
                                           A FALSE 0.00 0.00
                                   Α
      1 2006.80 56.80
                        0.60
                                                              0.00 FALSE 0.00 0.00 0.00
                                   Α
                                           A FALSE 0.00 0.00
      1 2007.40 57.40
                        0.60
                                   Α
                                           A FALSE 0.00 0.00
                                                              0.00 FALSE 0.00 0.00 0.00
      1 2008.00 58.00
                        0.60
                                   Α
                                           A FALSE 0.00 0.00
                                                              0.00 FALSE 0.00 0.00 0.00
      1 2008.60 58.60
                        0.60
                                   Α
                                           A FALSE 0.00 0.00
                                                              0.00 FALSE 0.00 0.00 0.00
      1 2009.20 59.20
                        0.43
                                           A FALSE 0.00 0.00
                                                              0.00 FALSE 0.00 0.00 0.00
                                  Α
      1 2009.63 59.63
                                           A FALSE 0.00 0.00
                                                              0.00 TRUE 0.00 0.00 0.00
                        0.17
                                  Α
      1 2009.80 59.80
                        0.60
                                  Α
                                           A FALSE 0.00 0.00
                                                              0.00
                                                                    TRUE 0.17 0.17 0.07
      1 2010.40 60.40
                        0.60
                                  Α
                                           A FALSE 0.00 0.00
                                                              0.00
                                                                    TRUE 0.77 0.77 0.30
      1 2011.00 61.00
                        0.60
                                  Α
                                           A FALSE 0.00 0.00
                                                              0.00
                                                                    TRUE 1.37 1.37 0.53
                                  Α
                                                                    TRUE 1.97 1.97 0.76
      1 2011.60 61.60
                        0.60
                                           A FALSE 0.00 0.00
                                                              0.00
                                  Α
      1 2012.20 62.20
                        0.60
                                           A FALSE 0.00 0.00
                                                              0.00
                                                                    TRUE 2.57 2.57 1.00
                                  Α
      1 2012.80 62.80
                        0.19
                                           A FALSE 0.00 0.00
                                                              0.00
                                                                    TRUE 3.17 3.17 1.23
      1 2012.99 62.99
                        0.03
                                                              0.00
                                                                    TRUE 3.36 3.36 1.30
                                   Α
                                           A FALSE 0.00 0.00
      1 2013.02 63.02
                        0.38
                                   Α
                                           A FALSE 0.00 0.00
                                                              0.00
                                                                    TRUE 3.39 3.39 2.60
      1 2013.40 63.40
                                  Α
                                           A FALSE 0.00 0.00
                                                              0.00 TRUE 3.77 3.77 3.53
                        0.15
      1 2013.55 63.55
                        0.41
                                  Α
                                           A FALSE 0.00 0.00
                                                              0.00 FALSE 3.92 3.92 3.90
      1 2013.96 63.96
                        0.00
                                  Α
                                              TRUE 0.00 0.00
                                                              0.00 FALSE 4.33 3.92 3.90
                                           Α
      1 2013.96 63.96
                        0.04
                                              TRUE 0.00 0.00
                                                              0.00 FALSE 4.33 3.92 3.90
                                  Α
                                           Α
      1 2014.00 64.00
                        0.25
                                              TRUE 0.04 0.04
                                                              0.50 FALSE 4.37 3.92 3.90
                                   Α
                                           Α
      1 2014.25 64.25
                        0.00
                                   Α
                                              TRUE 0.29 0.29
                                                              4.00 FALSE 4.62 3.92 3.90
                                           Α
      1 2014.25 64.25
                                              TRUE 0.29 0.29
                        0.26
                                   Α
                                           Α
                                                              4.00 FALSE 4.62 3.92 3.90
       2014.51 64.51
                        0.00
                                   Α
                                              TRUE 0.54 0.54
                                                              8.00 FALSE 4.88 3.92 3.90
                                           Α
      1 2014.51 64.51
                        0.09
                                   Α
                                           Α
                                              TRUE 0.54 0.54 8.00 FALSE 4.88 3.92 3.90
      1 2014.60 64.60
                        0.39
                                   Α
                                           A TRUE 0.64 0.64 8.57 FALSE 4.97 3.92 3.90
      1 2014.99 64.99
                        0.00
                                   Α
                                           A TRUE 1.03 1.03 11.00 FALSE 5.36 3.92 3.90
      1 2014.99 64.99
                                           A TRUE 1.03 1.03 11.00 FALSE 5.36 3.92 3.90
                        0.01
                                   Α
      2 2008.00 57.00
                        0.60
                                  Α
                                           A TRUE 0.00 0.40 0.31 FALSE 0.00 0.00 0.00
                                                              0.77 FALSE 0.00 0.00 0.00
      2 2008.60 57.60
                        0.49
                                  Α
                                           A TRUE 0.60 1.00
      2 2009.09 58.09
                        0.11
                                           A TRUE 1.09 1.49
                                                              1.14 TRUE 0.00 0.00 0.00
                                  Α
      2 2009.20 58.20
                        0.60
                                  Α
                                              TRUE 1.20 1.60
                                                              1.23
                                                                    TRUE 0.11 0.11 0.06
                                           Α
                                           Α
      2 2009.80 58.80
                        0.60
                                   Α
                                              TRUE 1.80 2.20
                                                              1.68
                                                                    TRUE 0.71 0.71 0.37
      2 2010.40 59.40
                        0.60
                                   Α
                                              TRUE 2.40 2.80 2.14 TRUE 1.31 1.31 0.68
```

```
Α
           2 2011.00 60.00
                                             0.52
                                                                              A TRUE 3.00 3.40 2.60 TRUE 1.91 1.91 0.99
           2 2011.52 60.52
                                            0.00
                                                             Α
                                                                               A FALSE 3.52 3.93 3.00
                                                                                                                            TRUE 2.43 2.43 1.26
                                                              Α
           2 2011.52 60.52
                                         0.08
                                                                              A FALSE 3.52 3.93
                                                                                                                3.00
                                                                                                                            TRUE 2.43 2.43 1.26
         Α
           2 2011.60 60.60
                                        0.00
                                                                             A FALSE 3.60 3.93
                                                                                                                3.00
                                                                                                                            TRUE 2.51 2.51 1.30
           2 2017.60 66.60
                                                                              A FALSE 9.60 6.69 18.00 TRUE 8.51 7.40 4.64
                                            0.04
                                                              Α
           2 2017.64 66.64 0.36
                                                              Α
                                                                              D FALSE 9.64 6.69 18.00 FALSE 8.55 7.43 4.70
> dos <- addDrug.Lexis(Sx, pdat, method = "dos", dpt = 6)</pre>
NOTE: timescale taken as 'per'
NOTE: end of exposure based on purchase and dosage (dpt).
> summary(dos)
Transitions:
        То
From A D Records: Events: Risk time: Persons:
     A 66 1 67
                                      1 19
> print(dos, nd = 2)
                                age lex.dur lex.Cst lex.Xst F.ex F.tf F.ct F.cd G.ex G.tf G.ct G.cd
                   per
           1 2006.00 56.00
                                            0.20 A
                                                                        A FALSE 0.00 0.00 0.00 FALSE 0.00 0.00 0.00

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 0.00 0.00 0.00

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 0.00 0.00 0.00

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 0.00 0.00 0.00

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 0.00 0.00 0.00

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 0.00 0.00 0.00

      0.43
      A
      A FALSE 0.00 0.00 0.00 FALSE 0.00 0.00 0.00

      0.17
      A
      A FALSE 0.00 0.00 0.00 TRUE 0.00 0.00 0.00

      0.05
      A
      A FALSE 0.00 0.00 0.00 FALSE 0.22 0.22 1.30

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 0.22 0.22 1.30

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 1.37 0.22 1.30

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 1.37 0.22 1.30

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 1.37 0.22 1.30

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 1.37 0.22 1.30

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 1.37 0.22 1.30

      0.60
      A
      A FALSE 0.00 0.00 0.00 FALSE 3.17 0.22 1.30

      0.19
      A
      A FALSE 0.00 0.00 0.00 FALSE 3.17 0.22 1.30

           1 2006.20 56.20
                                             0.60
                                                                              A FALSE 0.00 0.00 0.00 FALSE 0.00 0.00 0.00
                                                              Α
           1 2006.80 56.80
           1 2007.40 57.40
           1 2008.00 58.00
           1 2008.60 58.60
           1 2009.20 59.20
           1 2009.63 59.63
          1 2009.80 59.80
           1 2009.85 59.85
           1 2010.40 60.40
          1 2011.00 61.00
           1 2011.60 61.60
           1 2012.20 62.20
           1 2012.80 62.80
           1 2012.99 62.99
```

```
Α
2 2017.00 66.00
            0.17
                          A FALSE 9.00 2.19 18.00 TRUE 7.91 0.59 3.70
                    Α
                          A FALSE 9.17 2.19 18.00 FALSE 8.08 0.76 4.70
2 2017.17 66.17
             0.43
2 2017.60 66.60
             0.40
                          D FALSE 9.60 2.19 18.00 FALSE 8.51 0.76 4.70
                     Α
```

> fix <- addDrug.Lexis(Sx, pdat, method = "fix", maxt = 1)</pre>

NOTE: timescale taken as 'per'

Values of maxt has been recycled across 2 drugs

NOTE: end of exposure based on fixed coverage time of 1 .

> summary(fix)

```
Transitions:
  То
From A D Records: Events: Risk time: Persons:
 A 63 1 64 1 19
> print(fix, nd = 2)
   lex.id
      per age lex.dur lex.Cst lex.Xst F.ex F.tf F.ct F.cd G.ex G.tf G.ct G.cd
                    A A FALSE 0.00 0.00 0.00 FALSE 0.00 0.00 0.00
    1 2006.00 56.00
              0.20
```

```
2 2013.93 62.93
                  0.07
                                       TRUE 5.93 3.17 16.00 FALSE 4.84 2.00 2.00
2 2014.00 63.00
                  0.57
                                       TRUE 6.00 3.24 16.14 FALSE 4.91 2.00 2.00
                            Α
2 2014.57 63.57
                 0.03
                            Α
                                    Α
                                       TRUE 6.57 3.80 17.27
                                                            TRUE 5.48 2.00 2.00
                                                            TRUE 5.51 2.03 2.03
2 2014.60 63.60
                  0.33
                           Α
                                    A TRUE 6.60 3.84 17.34
2 2014.93 63.93
                 0.27
                           Α
                                    A FALSE 6.93 4.17 18.00 TRUE 5.84 2.37 2.37
                0.37
2 2015.20 64.20
                           Α
                                   A FALSE 7.20 4.17 18.00 TRUE 6.11 2.63 2.63
2 2015.57 64.57
                 0.23
                           Α
                                   A FALSE 7.57 4.17 18.00 FALSE 6.48 3.00 3.00
                                   A FALSE 7.80 4.17 18.00 FALSE 6.71 3.00 3.00
2 2015.80 64.80
                 0.60
                           Α
2 2016.40 65.40
                 0.51
                           Α
                                   A FALSE 8.40 4.17 18.00 FALSE 7.31 3.00 3.00
2 2016.91 65.91
                           Α
                                   A FALSE 8.91 4.17 18.00 TRUE 7.82 3.00 3.00
                 0.09
                           Α
                                    A FALSE 9.00 4.17 18.00
2 2017.00 66.00
                                                            TRUE 7.91 3.09 3.67
                 0.00
2 2017.00 66.00
                  0.60
                                    A FALSE 9.00 4.17 18.00
                                                            TRUE 7.91 3.09 3.70
                            Α
2 2017.60 66.60
                  0.40
                            Α
                                    D FALSE 9.60 4.17 18.00 TRUE 8.51 3.69 4.30
```

3.2 A more realistic example with run times

3.2.1 Follow-up data: DMlate

As example data we use rows from the DMlate example data from the Epi package:

```
> data(DMlate) ; str(DMlate)
                     10000 obs. of 7 variables:
'data.frame':
 $ sex : Factor w/ 2 levels "M", "F": 2 1 2 2 1 2 1 1 2 1 ...
 $ dobth: num 1940 1939 1918 1965 1933 ...
 $ dodm : num 1999 2003 2005 2009 2009 ...
 $ dodth: num NA NA NA NA NA ...
 $ dooad: num NA 2007 NA NA NA ...
 $ doins: num    NA NA NA NA NA NA NA NA NA ...
 $ dox : num 2010 2010 2010 2010 2010 ...
> Lx <- Lexis(entry = list(per = dodm,
                           age = dodm - dobth,
                           tfd = 0),
               exit = list(per = dox),
        exit.status = factor(!is.na(dodth),
                             labels = c("DM", "Dead")),
               data = DMlate[sample(1:nrow(DMlate), 1000),])
NOTE: entry.status has been set to "DM" for all.
> summary(Lx)
Transitions:
     Tο
From DM Dead Records: Events: Risk time: Persons:
                                    5303.88
  DM 758 242
                   1000
                             242
                                                 1000
We split the data along the age-scale (omitting the variables we shall not need):
> Sx <- splitLexis(Lx[,1:7], time.scale="age", breaks = 0:120)
> summary(Sx)
Transitions:
     Tο
      DM Dead Records: Events: Risk time: Persons:
  DM 6044 242
                    6286 242
                                     5303.88
                                                  1000
> str(Sx)
```

```
Classes 'Lexis' and 'data.frame':
                                         6286 obs. of 7 variables:
 $ lex.id : int 1 1 1 1 2 2 2 3 3 3 ...
 $ per
         : num 1996 1996 1997 1998 2008 ...
          : num 75.51 76 77 78 7.51 ...
 $ age
         : num 0 0.49 1.49 2.49 0 ...
 $ tfd
 $ lex.dur: num 0.49 1 1 0.59 0.493 ...
 $ lex.Cst: Factor w/ 2 levels "DM", "Dead": 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Xst: Factor w/ 2 levels "DM", "Dead": 1 1 1 2 1 1 1 1 1 1 ...
 - attr(*, "breaks")=List of 3
  ..$ per: NULL
  ..$ age: int [1:121] 0 1 2 3 4 5 6 7 8 9 ...
  ..$ tfd: NULL
 - attr(*, "time.scales")= chr [1:3] "per" "age" "tfd"
 - attr(*, "time.since")= chr [1:3] "" ""
```

3.2.2 Artificial prescription data

To explore how addDrug.Lexis works, we need drug exposure data, but these are unfortunately not available, so we simulate three datasets representing purchases of three types of drugs:

```
> set.seed(1952)
> purA <-
   ( data.frame(lex.id = rep(Lx$lex.id,
                             round(runif(nrow(Lx), 0, 20))))
+ %>% left_join(Lx[,c("lex.id", "dodm", "dox")])
+ \%>% mutate(per = dodm + runif(length(dodm), -0.1, 0.99) * (dox - dodm),
            amt = sample(4:20*10, length(dodm), replace = TRUE),
            dpt = amt * round(runif(length(dodm), 3, 7)))
+ %>% select(-dodm, -dox)
+ %>% arrange(lex.id, per)
> addmargins(table(table(purA$lex.id)))
                 5
                     6
                        7
                                 9 10
                             8
                                       11
                                           12
                                               13 14
                                                       15
                                                           16
                                                               17
                                                                   18 19
                                                                           20 Sum
51 46 47 45 49 58 51 44 53 48
                                       50
                                           48
                                               54 64
                                                       52 47
                                                               37
                                                                   50 46
                                                                           28 968
> str(purA)
                    9942 obs. of 4 variables:
'data.frame':
$ lex.id: int 1 1 1 1 1 1 1 1 1 ...
        : num 1995 1996 1996 1996 ...
        : num 80 120 170 100 180 60 190 90 80 180 ...
              400 720 1020 300 1080 360 950 360 560 1080 ...
$ dpt
        : num
> purB <-
   ( data.frame(lex.id = rep(Lx$lex.id,
                             round(pmax(runif(nrow(Lx), -10, 15), 0))))
+ %>% left_join(Lx[,c("lex.id", "dodm", "dox")])
+ \%>% mutate(per = dodm + runif(length(dodm), -0.1, 0.99) * (dox - dodm),
            amt = sample(4:20*10, length(dodm), replace = TRUE),
            dpt = amt * round(runif(length(dodm), 5, 9)))
+ %>% select(-dodm, -dox)
+ %>% arrange(lex.id, per)
   ) -> purB
> addmargins(table(table(purB$lex.id)))
                                 9
                             8
                                   10
                                       11
                                           12 13 14
                                                       15 Sum
   37 31 36 45 30 44 31 32 37 45
                                           48 31 48
```

```
> str(purB)
'data.frame':
                     4385 obs. of 4 variables:
               1 4 4 4 4 4 4 4 4 4 . . .
 $ lex.id: int
        : num 1997 2001 2001 2001 2002 ...
         : num 150 80 190 90 100 40 100 190 80 150 ...
         : num 1050 480 950 720 600 320 500 1520 480 1050 ...
 $ dpt
> purC <-
    ( data.frame(lex.id = rep(Lx$lex.id,
                              round(pmax(runif(nrow(Lx), -5, 12), 0))))
+ %>% left_join(Lx[,c("lex.id", "dodm", "dox")])
+ \%\% mutate(per = dodm + runif(length(dodm), -0.1, 0.99) * (dox - dodm),
             amt = sample(4:20*10, length(dodm), replace = TRUE),
             dpt = amt * round(runif(length(dodm), 5, 7)))
+ %>% select(-dodm, -dox)
+ %>% arrange(lex.id, per)
> addmargins(table(table(purC$lex.id)))
              4
                  5
                      6
                          7
                              8
                                  9
                                    10
                                         11
                                             12 Sum
    68
            55
                 48
                     59
                         48
                            47
                                 56
                                    46 72 27 641
> str(purC)
'data.frame':
                     3961 obs. of 4 variables:
 $ lex.id: int 1 1 1 1 1 1 4 4 4 4 ...
       : num 1996 1996 1998 1998 ...
 $ per
         : num 60 50 60 90 130 40 140 150 180 140 ...
        : num 360 300 300 540 780 240 840 900 1080 980 ...
> head(purC)
  lex.id
              per amt dpt
      1 1995.663 60 360
1
       1 1996.442
                  50 300
3
       1 1997.673 60 300
       1 1997.855 90 540
5
       1 1998.321 130 780
       1 1998.431 40 240
```

Note that the time scale is in years, so the dpt must be in amount per year, so that dpt/amt is the approximate number of annual drug purchases.

We now have three artificial drug purchase datasets so we can see how addDrug.Lexis performs on larger datasets:

3.2.3 Using addDrug

100 and 500 persons

We start out with a small sample and a three month grace period to limit the number of gaps:

```
Values of grace has been recycled across 3 drugs
NOTE: end of exposure based on differences in purchase times (per)
 and amount purchased (amt).
         system forløbet
  bruger
    4.07
            0.18
> summary(Sx1)
Transitions:
    Τо
From DM Dead Records: Events: Risk time: Persons:
  DM 644
          23
                   667
                           23
                                572.58
> summary(ad1)
Transitions:
    Tο
From DM Dead Records: Events: Risk time:
                                             Persons:
 DM 3051
           23
                   3074
                              23
                                     572.58
```

We then cut the number of persons in half to assess how run time depends on no. of persons in the data:

```
> Sx2 \leftarrow subset(Sx, lex.id < 500)
> pur <- list(A = subset(purA, lex.id < 500),
              B = subset(purB, lex.id < 500),
              C = subset(purC, lex.id < 500))
> system.time(ad2 <- addDrug.Lexis(Sx2, pur, tnam = "per", grace = 1/6))
Values of grace has been recycled across 3 drugs
NOTE: end of exposure based on differences in purchase times (per)
 and amount purchased (amt).
  bruger
           system forløbet
   13.03
             0.61
                     13.59
> summary(Sx2)
Transitions:
     Τo
From DM Dead Records: Events: Risk time: Persons:
  DM 3026 119
                    3145
                             119
                                     2657.01
> summary(ad2)
Transitions:
        DM Dead Records:
                           Events: Risk time: Persons:
From
  DM 14734 119
                    14853
                               119
                                      2657.01
```

... timing is broadly proportional to the number of persons.

Fewer prescription records

We can try to cut the number of purchases in half:

```
Values of grace has been recycled across 3 drugs
NOTE: end of exposure based on differences in purchase times (per)
 and amount purchased (amt).
         system forløbet
  bruger
    1.39
            0.16
                      1.55
> summary(Sx1)
Transitions:
     Tο
From DM Dead Records: Events: Risk time:
  DM 644
           23
                    667
                              23
                                     572.58
> summary(ad3)
Transitions:
    Τо
      DM Dead
               Records:
                          Events: Risk time:
  DM 2027
                    2050
                               23
                                      572.58
            23
```

It also appears that the number of purchases per person is also a determinant of the run time too; the timing is largely proportional to the number of drug records.

In any concrete application it is recommended to run the function on a fairly small sample of persons, say 1000 to get a feel for the run time. It may also be a good idea to run the function on chunks of the persons, to make sure that you do not lose all the processed data in a crash.

Fewer prescription types

Finally we try to cut the number of drugs, to assess how this influences the run time:

```
> pur <- list(B = subset(purB, lex.id < 100),</pre>
              C = subset(purC, lex.id < 100))</pre>
> sapply(pur, nrow)
  В
      С
558 307
> system.time(ad4 <- addDrug.Lexis(Sx1, pur, tnam = "per", grace = 1/6))
Values of grace has been recycled across 2 drugs
NOTE: end of exposure based on differences in purchase times (per)
 and amount purchased (amt).
           system forløbet
  bruger
    1.34
             0.03
                       1.37
> summary(Sx1)
Transitions:
     То
From DM Dead Records: Events: Risk time:
  DM 644
           23
                    667
                              23
                                      572.58
> summary(ad4)
Transitions:
     То
                           Events: Risk time:
From DM Dead Records:
                                                Persons:
  DM 1855
            23
                    1878
                                23
                                       572.58
                                                      99
```

We see that the number of drugs also influence the run time proportionally.

3.2.4 Too many records —coarse.Lexis

If we look at the length of the intervals as given in lex.dur we see that some are quite small:

```
> summary(ad1$lex.dur)
   Min. 1st Qu. Median Mean 3rd Qu. Max.
0.00000 0.03178 0.10877 0.18626 0.26397 1.00000
```

Half are smaller then 0.11 years, 40 days. We could without much loss of precision in the analysis based on the Lexis object merge adjacent records that have total risk time less than 3 months.

The function coarse.Lexis will collapse records with short lex.dur with the subsequent record. The collapsing will use the covariates from the first record, and so the entire follow-up from the two records will have the characteristics of the first. Therefore it is wise to choose first records with reasonably short lex.dur—the approximation will be better than if the first record was with a larger lex.dur. Therefore there are two values supplied to coarse.Lexis; the maximal length of the first record's lex.dur and the maximal length of the lex.dur in the resulting combined record. The larger these parameters are, the more the Lexis object is coarsened.

```
> summary(ad1)
Transitions:
     То
From
     DM Dead
                Records:
                           Events: Risk time:
  DM 3051
            23
                    3074
                                23
                                       572.58
> summary(adc <- coarse.Lexis(ad1, lim = c(1/6,1/2)))
Transitions:
     Τо
                Records:
From
       DM Dead
                           Events: Risk time:
                                                Persons:
  DM 1593
            23
                    1616
                                23
                                       572.58
                                                      99
> summary(adc$lex.dur)
   Min. 1st Qu.
                            Mean 3rd Qu.
                 Median
 0.0000 0.2060
                 0.3072
                          0.3543
                                 0.4420
```

This could cut the number of units for analysis substantially, in this case from about 27,000 to some 13,000.

Records to be kept

When we are dealing with drug exposure data we will be interested keeping the record that holds the start of a drug exposure. Some may argue that it does not matter much, though.

The records (*i.e.* beginnings of FU intervals) that should be kept must be given in logical vector in the argument keep:

```
> summary(Sx2)
Transitions:
    To
From DM Dead Records: Events: Risk time: Persons:
    DM 3026 119 3145 119 2657.01 499
```

```
> system.time(ad4 <- addDrug.Lexis(Sx2,
                                 tnam = "per",
+
                                grace = 1/6)
Values of grace has been recycled across 2 drugs
NOTE: end of exposure based on differences in purchase times (per)
 and amount purchased (amt).
          system forløbet
  bruger
            0.12
    2.85
                     2.96
> summary(ad4)
Transitions:
    Tο
From DM Dead Records: Events: Risk time: Persons:
  DM 4237 119
                                                  499
               4356
                         119 2657.01
> #
> ad5 <- coarse.Lexis(ad4,
                     \lim = c(1/4, 1/2)
> summary(ad5)
Transitions:
    Tο
From DM Dead Records: Events: Risk time: Persons:
  DM 3497 119
                   3616
                             119
                                    2657.01
                                                  499
```

We can identify the first date of exposure to drug B, say, by the exposure (B.ex) being true and the cumulative time on the drug (B.ct) being 0:

We see the expected behaviour when we use coarse.Lexis: we get fewer records, but identical follow-up. And the keep argument gives the possibility to keep selected records, or more precisely beginnings. keep prevents a record to be collapsed with a previous one, but not with a subsequent one.

```
Start time: 2024-05-27, 17:08:12
End time: 2024-05-27, 17:08:40
Elapsed time: 0.47 minutes
```

Bibliography

- [1] B Carstensen. Age-Period-Cohort models for the Lexis diagram. *Statistics in Medicine*, 26(15):3018–3045, 2007.
- [2] B Carstensen, JK Kristensen, P Ottosen, and K Borch-Johnsen. The Danish National Diabetes Register: Trends in incidence, prevalence and mortality. *Diabetologia*, 51:2187–2196, 2008.