

Time dependent covariates in Lexis objects

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Chapter 1

Overview and rationale

This note describes the functions `addCov.Lexis` and `addDrug.Lexis` designed to add values of clinical measurements and drug exposures 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`. But the purposes of the two functions here are to append quantitative variables that in principle can take any (positive) value. Adding new states at intermediate events is the business of `cutLexis`.

Both functions are so-called S3 methods for `Lexis` objects, so in code you can omit the “`.Lexis`”. Note that neither `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 to 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 present with 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.

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"),
+                          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)
> xcoh$doe <- cal.yr(xcoh$entry)
> xcoh$dox <- cal.yr(xcoh$exit )
> xcoh
```

	id	birth	entry	exit	fail	dob	doe	dox
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
3	C	1987-06-10	1991-12-23	1998-07-24	1	1987.437	1991.974	1998.559

2.2.1 A Lexis object

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

```
> Lcoh <- Lexis(entry = list(per = doe),
+                 exit = list(per = dox,
+                             age = dox - dob),
+                 id = id,
```

```

+       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
 $ age      : '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   : Factor w/ 3 levels "A","B","C": 1 2 3
 $ id      : chr  "A" "B" "C"
 $ birth   : chr  "1952-07-14" "1954-04-01" "1987-06-10"
 $ entry   : chr  "1965-08-04" "1972-09-08" "1991-12-23"
 $ exit    : chr  "1997-06-27" "1995-05-23" "1998-07-24"
 $ fail    : num  1 0 1
 $ dob     : 'cal.yr' num  1953 1954 1987
 $ doe     : 'cal.yr' num  1966 1973 1992
 $ dox     : 'cal.yr' num  1997 1995 1999
 - attr(*, "time.scales")= chr  "per" "age"
 - attr(*, "time.since")= chr  "" ""
 - attr(*, "breaks")=List of 2
 ..$ per: NULL
 ..$ age: NULL
> (Lx <- Lcoh[,1:6])
lex.id    per    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.

```

> Lx$lex.id <- as.character(Lx$lex.id)
> str(Lx)
Classes 'Lexis' and 'data.frame':      3 obs. of  6 variables:
 $ per      : 'cal.yr' num  1966 1973 1992
 $ age      : '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"
 - attr(*, "time.scales")= chr  "per" "age"
 - attr(*, "time.since")= chr  "" ""
 - attr(*, "breaks")=List of 2
 ..$ per: NULL
 ..$ age: NULL

```

```
> Lx
lex.id    per    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
```

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:
 $ lex.id: chr  "A" "A" "C" "B" ...
 $ per   : 'cal.yr' num  1977 1974 1996 1991 1989
 $ bp    : num   120 140 160 157 145
 $ chol  : num    NA  5  8  9  6
 $ xnam  : chr   "X2" "X1" "X1" "X2" ...
> clin
lex.id    per    bp chol xnam
1      A 1977.206 120   NA  X2
2      A 1973.573 140    5  X1
3      C 1996.163 160    8  X1
4      B 1990.531 157    9  X2
5      C 1989.083 145    6  X0
```

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))
lex.id    per    age  tfc lex.dur lex.Cst lex.Xst exnam  bp chol xnam
  A 1965.59 13.06   NA   7.98   Alive   Alive  <NA>   NA  NA  <NA>
  A 1973.57 21.04  0.00   3.63   Alive   Alive  ex1 140    5   X1
  A 1977.21 24.67  0.00  20.28   Alive   Dead  ex2 120   NA   X2
  B 1972.69 18.44   NA  17.85   Alive   Alive  <NA>   NA  NA  <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   Alive   Alive  ex1 145    6   X0
  C 1996.16  8.73  0.00   2.40   Alive   Dead  ex2 160    8   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"))
lex.id    per   age tfCl lex.dur lex.Cst lex.Xst xnam  bp chol
      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  NA   17.85   Alive   Alive <NA>  NA   NA
      B 1990.53 36.28 0.00    4.86   Alive   Alive  X2 157    9
      C 1991.97  4.54 2.89    4.19   Alive   Alive  X0 145    6
      C 1996.16  8.73 0.00    2.40   Alive   Dead  X1 160    8

> summary(Dx, t=T)
Transitions:
      To
From    Alive Dead Records: Events: Risk time: Persons:
  Alive      5    2         7         2    61.18         3

Timescales:
per age tfCl
""  ""  "x"
```

2.3 Exchanging split and add

As noted in the beginning of this not `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
lex.id    per   age   tfc lex.dur lex.Cst lex.Xst xnam  bp chol
      A 1965.59 13.06   NA    1.94   Alive   Alive <NA>  NA   NA
      A 1967.53 15.00   NA    5.00   Alive   Alive <NA>  NA   NA
      A 1972.53 20.00   NA    1.04   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    0.33   Alive   Alive  X2 120   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   NA
      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   NA
```

```

      B 1979.25 25.00    NA    5.00   Alive   Alive <NA>   NA    NA
      B 1984.25 30.00    NA    5.00   Alive   Alive <NA>   NA    NA
      B 1989.25 35.00    NA    1.28   Alive   Alive <NA>   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
      C 1991.97  4.54  2.89    0.46   Alive   Alive    X0 145    6
      C 1992.44  5.00  3.35    3.73   Alive   Alive    X0 145    6
      C 1996.16  8.73  0.00    1.27   Alive   Alive    X1 160    8
      C 1997.44 10.00  1.27    1.12   Alive    Dead    X1 160    8

> #
> # split AFTER add
> La <- splitLexis(addCov.Lexis(Lx,
+                               clin,
+                               exnam = "xnam" ),
+                               time.scale = "age",
+                               breaks = seq(0, 80, 5))
> La
lex.id    per   age   tfc lex.dur lex.Cst lex.Xst xnam   bp chol
A 1965.59 13.06    NA   1.94   Alive   Alive <NA>   NA    NA
A 1967.53 15.00    NA   5.00   Alive   Alive <NA>   NA    NA
A 1972.53 20.00    NA   1.04   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   0.33   Alive   Alive    X2 120    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    NA
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    NA
B 1979.25 25.00    NA   5.00   Alive   Alive <NA>   NA    NA
B 1984.25 30.00    NA   5.00   Alive   Alive <NA>   NA    NA
B 1989.25 35.00    NA   1.28   Alive   Alive <NA>   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
C 1991.97  4.54  2.89    0.46   Alive   Alive    X0 145    6
C 1992.44  5.00  3.35    3.73   Alive   Alive    X0 145    6
C 1996.16  8.73  0.00    1.27   Alive   Alive    X1 160    8
C 1997.44 10.00  1.27    1.12   Alive    Dead    X1 160    8

```

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:

```

> La$tfc == Lb$tfc
[1] NA NA NA TRUE TRUE TRUE TRUE TRUE TRUE NA NA NA NA NA TRUE TRUE TRUE
[18] TRUE TRUE TRUE

> La$age == Lb$age
[1] TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE
[18] TRUE TRUE TRUE

> La$per == Lb$per
[1] TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE
[18] TRUE TRUE TRUE

```

The same goes for `splitMulti`:


```

> if (require(popEpi, quietly=TRUE)) {
+   ## 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
+   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:

```

> if (require(tidyr, quietly=TRUE)) {
+   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:

```

> if (require(tidyr, quietly=TRUE)) {
+   Lx <- La
+   Lx[,cov] <- as.data.frame( group_by(Lx, lex.id)
+                             %>% fill(all_of(cov)))[,cov]
+   class(Lx)
+   La
+   Lx
+ }

```

lex.id	per	age	tfc	lex.dur	lex.Cst	lex.Xst	xnam	bp	chol
A 1965.59	13.06	NA	1.94	Alive	Alive	<NA>	NA	NA	
A 1967.53	15.00	NA	5.00	Alive	Alive	<NA>	NA	NA	
A 1972.53	20.00	NA	1.04	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	0.33	Alive	Alive	X2	120	5	

A	1977.53	25.00	0.33	5.00	Alive	Alive	X2 120	5
A	1982.53	30.00	5.33	5.00	Alive	Alive	X2 120	5
A	1987.53	35.00	10.33	5.00	Alive	Alive	X2 120	5
A	1992.53	40.00	15.33	4.95	Alive	Dead	X2 120	5
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	NA
B	1979.25	25.00	NA	5.00	Alive	Alive	<NA> NA	NA
B	1984.25	30.00	NA	5.00	Alive	Alive	<NA> NA	NA
B	1989.25	35.00	NA	1.28	Alive	Alive	<NA> 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
C	1991.97	4.54	2.89	0.46	Alive	Alive	X0 145	6
C	1992.44	5.00	3.35	3.73	Alive	Alive	X0 145	6
C	1996.16	8.73	0.00	1.27	Alive	Alive	X1 160	8
C	1997.44	10.00	1.27	1.12	Alive	Dead	X1 160	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 variable any more; the 5 in `chol` is measured in 1971.5 but `tfc` is reset to 0 at 1977.3, despite 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 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 <- splitLexis(Lx, "per", breaks = seq(1990, 2020, 0.6))
> summary(Sx)
Transitions:
      To
From A D Records: Events: Risk time: Persons:
  A 32 1         33         1         19         2
> str(Sx)
Classes 'Lexis' and 'data.frame':      33 obs. of  6 variables:
 $ lex.id : int  1 1 1 1 1 1 1 1 1 1 ...
 $ per    : num  2006 2006 2007 2007 2008 ...
 $ age    : 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 ...
 - attr(*, "breaks")=List of 2
 ..$ per: num  1990 1991 1991 1992 1992 ...
 ..$ age: NULL
 - attr(*, "time.scales")= chr  "per" "age"
 - attr(*, "time.since")= chr  "" ""
```

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

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

```
> set.seed(1952)
> rf <- data.frame(per = c(2005 + runif(12, 0, 10)),
+                 amt = sample(2:4, 12, replace = TRUE),
+                 lex.id = sample(1:2, 12, replace = TRUE)) %>%
+   arrange(lex.id, per)
> rg <- data.frame(per = c(2009 + runif(10, 0, 10)),
+                 amt = sample(round(2:4/3,1), 10, replace = TRUE),
+                 lex.id = sample(1:2, 10, replace = TRUE)) %>%
+   arrange(lex.id, per)
```

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.

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, the names will be used as prefixes of the generated exposure variables. We can show the resulting data:

```
> pdat <- list(F = rf, G = rg)
> pdat
$F
      per amt lex.id
1 2013.964  4      1
2 2014.251  4      1
3 2014.509  3      1
4 2014.990  2      1
5 2005.311  2      2
```

```

6  2007.595  3      2
7  2011.710  4      2
8  2011.812  3      2
9  2012.865  2      2
10 2013.331  2      2
11 2013.417  2      2
12 2013.932  2      2

```

\$G

```

      per amt lex.id
1  2009.630 1.3      1
2  2012.987 1.3      1
3  2013.018 1.3      1
4  2016.954 0.7      1
5  2017.924 1.0      1
6  2009.089 1.3      2
7  2011.599 0.7      2
8  2014.566 1.0      2
9  2016.912 0.7      2
10 2017.004 1.0      2

```

> Lx

```

lex.id  per age lex.dur lex.Cst lex.Xst
      1 2006  56      9      A      A
      2 2008  57     10      A      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:

```

      To
From  A D  Records:  Events: Risk time:  Persons:
      A 32 1      33      1      19      2
[1] "lex.id" "per"      "age"      "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:

```

      To
From  A D  Records:  Events: Risk time:  Persons:
      A 64 1      65      1      19      2
[1] "lex.id" "per"      "age"      "lex.dur" "lex.Cst" "lex.Xst" "F.ex"      "F.tf"
[9] "F.ct"     "F.cd"     "G.ex"     "G.tf"     "G.ct"     "G.cd"

```

> `ex1`

```

lex.id  per  age lex.dur lex.Cst lex.Xst  F.ex  F.tf  F.ct  F.cd  G.ex  G.tf  G.ct
      1 2006.00 56.00   0.20      A      A FALSE 0.000 0.000 0.000 FALSE 0.000 0.000
      1 2006.20 56.20   0.60      A      A FALSE 0.000 0.000 0.000 FALSE 0.000 0.000
      1 2006.80 56.80   0.60      A      A FALSE 0.000 0.000 0.000 FALSE 0.000 0.000

```

1	2007.40	57.40	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2008.00	58.00	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2008.60	58.60	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2009.20	59.20	0.43	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2009.63	59.63	0.17	A	A	FALSE	0.000	0.000	0.000	TRUE	0.000	0.000
1	2009.80	59.80	0.60	A	A	FALSE	0.000	0.000	0.000	TRUE	0.170	0.170
1	2010.40	60.40	0.60	A	A	FALSE	0.000	0.000	0.000	TRUE	0.770	0.770
1	2011.00	61.00	0.60	A	A	FALSE	0.000	0.000	0.000	TRUE	1.370	1.370
1	2011.60	61.60	0.60	A	A	FALSE	0.000	0.000	0.000	TRUE	1.970	1.970
1	2012.20	62.20	0.60	A	A	FALSE	0.000	0.000	0.000	TRUE	2.570	2.570
1	2012.80	62.80	0.19	A	A	FALSE	0.000	0.000	0.000	TRUE	3.170	3.170
1	2012.99	62.99	0.03	A	A	FALSE	0.000	0.000	0.000	TRUE	3.357	3.357
1	2013.02	63.02	0.03	A	A	FALSE	0.000	0.000	0.000	TRUE	3.388	3.388
1	2013.05	63.05	0.35	A	A	FALSE	0.000	0.000	0.000	FALSE	3.420	3.420
1	2013.40	63.40	0.56	A	A	FALSE	0.000	0.000	0.000	FALSE	3.770	3.420
1	2013.96	63.96	0.00	A	A	TRUE	0.000	0.000	0.000	FALSE	4.334	3.420
1	2013.96	63.96	0.04	A	A	TRUE	0.000	0.000	0.000	FALSE	4.334	3.420
1	2014.00	64.00	0.25	A	A	TRUE	0.036	0.036	0.497	FALSE	4.370	3.420
1	2014.25	64.25	0.00	A	A	TRUE	0.286	0.286	4.000	FALSE	4.621	3.420
1	2014.25	64.25	0.26	A	A	TRUE	0.286	0.286	4.000	FALSE	4.621	3.420
1	2014.51	64.51	0.00	A	A	TRUE	0.545	0.545	8.000	FALSE	4.879	3.420
1	2014.51	64.51	0.09	A	A	TRUE	0.545	0.545	8.000	FALSE	4.879	3.420
1	2014.60	64.60	0.10	A	A	TRUE	0.636	0.636	9.406	FALSE	4.970	3.420
1	2014.70	64.70	0.00	A	A	FALSE	0.739	0.739	11.000	FALSE	5.073	3.420
1	2014.70	64.70	0.29	A	A	FALSE	0.739	0.739	11.000	FALSE	5.073	3.420
1	2014.99	64.99	0.01	A	A	TRUE	1.025	0.739	11.000	FALSE	5.360	3.420
2	2008.00	57.00	0.60	A	A	TRUE	0.000	0.405	0.354	FALSE	0.000	0.000
2	2008.60	57.60	0.49	A	A	TRUE	0.600	1.005	0.879	FALSE	0.000	0.000
2	2009.09	58.09	0.11	A	A	TRUE	1.089	1.494	1.308	TRUE	0.000	0.000
2	2009.20	58.20	0.60	A	A	TRUE	1.200	1.605	1.405	TRUE	0.111	0.111
2	2009.80	58.80	0.60	A	A	TRUE	1.800	2.205	1.930	TRUE	0.711	0.711
2	2010.40	59.40	0.60	A	A	TRUE	2.400	2.805	2.455	TRUE	1.311	1.311
2	2011.00	60.00	0.02	A	A	TRUE	3.000	3.405	2.981	TRUE	1.911	1.911
2	2011.02	60.02	0.00	A	A	FALSE	3.022	3.427	3.000	TRUE	1.933	1.933
2	2011.02	60.02	0.58	A	A	FALSE	3.022	3.427	3.000	TRUE	1.933	1.933
2	2011.60	60.60	0.00	A	A	FALSE	3.599	3.427	3.000	TRUE	2.510	2.510
2	2011.60	60.60	0.11	A	A	FALSE	3.600	3.427	3.000	TRUE	2.511	2.511
2	2011.71	60.71	0.00	A	A	TRUE	3.710	3.427	3.000	TRUE	2.621	2.621
2	2011.71	60.71	0.10	A	A	TRUE	3.710	3.427	3.000	TRUE	2.621	2.621
2	2011.81	60.81	0.08	A	A	TRUE	3.812	3.529	7.000	TRUE	2.723	2.723
2	2011.89	60.89	0.31	A	A	FALSE	3.889	3.605	10.000	TRUE	2.800	2.800
2	2012.20	61.20	0.60	A	A	FALSE	4.200	3.605	10.000	TRUE	3.111	3.111
2	2012.80	61.80	0.07	A	A	FALSE	4.800	3.605	10.000	TRUE	3.711	3.711
2	2012.87	61.87	0.09	A	A	TRUE	4.865	3.605	10.000	TRUE	3.776	3.776
2	2012.95	61.95	0.38	A	A	TRUE	4.951	3.691	10.368	FALSE	3.862	3.862
2	2013.33	62.33	0.07	A	A	TRUE	5.331	4.071	12.000	FALSE	4.242	3.862
2	2013.40	62.40	0.02	A	A	TRUE	5.400	4.140	13.606	FALSE	4.311	3.862
2	2013.42	62.42	0.09	A	A	TRUE	5.417	4.157	14.000	FALSE	4.328	3.862
2	2013.50	62.50	0.43	A	A	FALSE	5.503	4.243	16.000	FALSE	4.414	3.862
2	2013.93	62.93	0.07	A	A	TRUE	5.932	4.243	16.000	FALSE	4.843	3.862
2	2014.00	63.00	0.45	A	A	TRUE	6.000	4.311	16.265	FALSE	4.911	3.862
2	2014.45	63.45	0.12	A	A	FALSE	6.447	4.758	18.000	FALSE	5.357	3.862
2	2014.57	63.57	0.03	A	A	FALSE	6.566	4.758	18.000	TRUE	5.477	3.862
2	2014.60	63.60	0.60	A	A	FALSE	6.600	4.758	18.000	TRUE	5.511	3.895
2	2015.20	64.20	0.60	A	A	FALSE	7.200	4.758	18.000	TRUE	6.111	4.495
2	2015.80	64.80	0.60	A	A	FALSE	7.800	4.758	18.000	TRUE	6.711	5.095
2	2016.40	65.40	0.51	A	A	FALSE	8.400	4.758	18.000	TRUE	7.311	5.695

2	2016.91	65.91	0.09	A	A	FALSE	8.912	4.758	18.000	TRUE	7.822	6.207
2	2017.00	66.00	0.00	A	A	FALSE	9.000	4.758	18.000	TRUE	7.911	6.295
2	2017.00	66.00	0.13	A	A	FALSE	9.004	4.758	18.000	TRUE	7.914	6.299
2	2017.14	66.14	0.46	A	A	FALSE	9.135	4.758	18.000	FALSE	8.046	6.430
2	2017.60	66.60	0.40	A	D	FALSE	9.600	4.758	18.000	FALSE	8.511	6.430

G.cd
0.000
0.000
0.000
0.000
0.000
0.000
0.000
0.000
0.000
0.066
0.298
0.531
0.763
0.995
1.228
1.300
2.600
3.900
3.900
3.900
3.900
3.900
3.900
3.900
3.900
3.900
3.900
3.900
3.900
3.900
3.900
3.900
0.000
0.000
0.000
0.057
0.368
0.679
0.990
1.001
1.001
1.300
1.300
1.358
1.358
1.410
1.450
1.611
1.922
1.956
2.000
2.000
2.000
2.000

2.000
 2.000
 2.000
 2.000
 2.000
 2.014
 2.270
 2.526
 2.782
 3.000
 3.673
 3.700
 4.700
 4.700

```
> 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:

To

From A D Records: Events: Risk time: Persons:

A 62 1 63 1 19 2

```
> ex2
```

lex.id	per	age	lex.dur	lex.Cst	lex.Xst	F.ex	F.tf	F.ct	F.cd	G.ex	G.tf	G.ct
1	2006.00	56.00	0.20	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2006.20	56.20	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2006.80	56.80	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2007.40	57.40	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2008.00	58.00	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2008.60	58.60	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2009.20	59.20	0.43	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2009.63	59.63	0.17	A	A	FALSE	0.000	0.000	0.000	TRUE	0.000	0.000
1	2009.80	59.80	0.60	A	A	FALSE	0.000	0.000	0.000	TRUE	0.170	0.170
1	2010.40	60.40	0.60	A	A	FALSE	0.000	0.000	0.000	TRUE	0.770	0.770
1	2011.00	61.00	0.60	A	A	FALSE	0.000	0.000	0.000	TRUE	1.370	1.370
1	2011.60	61.60	0.60	A	A	FALSE	0.000	0.000	0.000	TRUE	1.970	1.970
1	2012.20	62.20	0.60	A	A	FALSE	0.000	0.000	0.000	TRUE	2.570	2.570
1	2012.80	62.80	0.19	A	A	FALSE	0.000	0.000	0.000	TRUE	3.170	3.170
1	2012.99	62.99	0.03	A	A	FALSE	0.000	0.000	0.000	TRUE	3.357	3.357
1	2013.02	63.02	0.38	A	A	FALSE	0.000	0.000	0.000	TRUE	3.388	3.388
1	2013.40	63.40	0.15	A	A	FALSE	0.000	0.000	0.000	TRUE	3.770	3.770
1	2013.55	63.55	0.41	A	A	FALSE	0.000	0.000	0.000	FALSE	3.920	3.920
1	2013.96	63.96	0.00	A	A	TRUE	0.000	0.000	0.000	FALSE	4.334	3.920
1	2013.96	63.96	0.04	A	A	TRUE	0.000	0.000	0.000	FALSE	4.334	3.920
1	2014.00	64.00	0.25	A	A	TRUE	0.036	0.036	0.497	FALSE	4.370	3.920
1	2014.25	64.25	0.00	A	A	TRUE	0.286	0.286	4.000	FALSE	4.621	3.920
1	2014.25	64.25	0.26	A	A	TRUE	0.286	0.286	4.000	FALSE	4.621	3.920
1	2014.51	64.51	0.00	A	A	TRUE	0.545	0.545	8.000	FALSE	4.879	3.920
1	2014.51	64.51	0.09	A	A	TRUE	0.545	0.545	8.000	FALSE	4.879	3.920
1	2014.60	64.60	0.39	A	A	TRUE	0.636	0.636	8.567	FALSE	4.970	3.920
1	2014.99	64.99	0.00	A	A	TRUE	1.025	1.025	11.000	FALSE	5.360	3.920
1	2014.99	64.99	0.01	A	A	TRUE	1.025	1.025	11.000	FALSE	5.360	3.920
2	2008.00	57.00	0.60	A	A	TRUE	0.000	0.405	0.309	FALSE	0.000	0.000

2	2008.60	57.60	0.49	A	A	TRUE	0.600	1.005	0.768	FALSE	0.000	0.000
2	2009.09	58.09	0.11	A	A	TRUE	1.089	1.494	1.141	TRUE	0.000	0.000
2	2009.20	58.20	0.60	A	A	TRUE	1.200	1.605	1.226	TRUE	0.111	0.111
2	2009.80	58.80	0.60	A	A	TRUE	1.800	2.205	1.684	TRUE	0.711	0.711
2	2010.40	59.40	0.60	A	A	TRUE	2.400	2.805	2.143	TRUE	1.311	1.311
2	2011.00	60.00	0.52	A	A	TRUE	3.000	3.405	2.601	TRUE	1.911	1.911
2	2011.52	60.52	0.00	A	A	FALSE	3.522	3.927	3.000	TRUE	2.433	2.433
2	2011.52	60.52	0.08	A	A	FALSE	3.522	3.927	3.000	TRUE	2.433	2.433
2	2011.60	60.60	0.00	A	A	FALSE	3.599	3.927	3.000	TRUE	2.510	2.510
2	2011.60	60.60	0.11	A	A	FALSE	3.600	3.927	3.000	TRUE	2.511	2.511
2	2011.71	60.71	0.00	A	A	TRUE	3.710	3.927	3.000	TRUE	2.621	2.621
2	2011.71	60.71	0.10	A	A	TRUE	3.710	3.927	3.000	TRUE	2.621	2.621
2	2011.81	60.81	0.39	A	A	TRUE	3.812	4.029	7.000	TRUE	2.723	2.723
2	2012.20	61.20	0.19	A	A	TRUE	4.200	4.416	9.017	TRUE	3.111	3.111
2	2012.39	61.39	0.41	A	A	FALSE	4.389	4.605	10.000	TRUE	3.300	3.300
2	2012.80	61.80	0.07	A	A	FALSE	4.800	4.605	10.000	TRUE	3.711	3.711
2	2012.87	61.87	0.47	A	A	TRUE	4.865	4.605	10.000	TRUE	3.776	3.776
2	2013.33	62.33	0.07	A	A	TRUE	5.331	5.071	12.000	TRUE	4.242	4.242
2	2013.40	62.40	0.02	A	A	TRUE	5.400	5.140	13.606	TRUE	4.311	4.311
2	2013.42	62.42	0.03	A	A	TRUE	5.417	5.157	14.000	TRUE	4.328	4.328
2	2013.45	62.45	0.48	A	A	TRUE	5.451	5.191	14.132	FALSE	4.362	4.362
2	2013.93	62.93	0.07	A	A	TRUE	5.932	5.672	16.000	FALSE	4.843	4.362
2	2014.00	63.00	0.57	A	A	TRUE	6.000	5.740	16.134	FALSE	4.911	4.362
2	2014.57	63.57	0.03	A	A	TRUE	6.566	6.306	17.251	TRUE	5.477	4.362
2	2014.60	63.60	0.35	A	A	TRUE	6.600	6.340	17.317	TRUE	5.511	4.395
2	2014.95	63.95	0.25	A	A	FALSE	6.947	6.687	18.000	TRUE	5.857	4.742
2	2015.20	64.20	0.60	A	A	FALSE	7.200	6.687	18.000	TRUE	6.111	4.995
2	2015.80	64.80	0.60	A	A	FALSE	7.800	6.687	18.000	TRUE	6.711	5.595
2	2016.40	65.40	0.51	A	A	FALSE	8.400	6.687	18.000	TRUE	7.311	6.195
2	2016.91	65.91	0.09	A	A	FALSE	8.912	6.687	18.000	TRUE	7.822	6.707
2	2017.00	66.00	0.00	A	A	FALSE	9.000	6.687	18.000	TRUE	7.911	6.795
2	2017.00	66.00	0.60	A	A	FALSE	9.004	6.687	18.000	TRUE	7.914	6.799
2	2017.60	66.60	0.04	A	A	FALSE	9.600	6.687	18.000	TRUE	8.511	7.395
2	2017.64	66.64	0.36	A	D	FALSE	9.635	6.687	18.000	FALSE	8.546	7.430

G.cd
0.000
0.000
0.000
0.000
0.000
0.000
0.000
0.000
0.000
0.066
0.298
0.531
0.763
0.995
1.228
1.300
2.600
3.534
3.900
3.900
3.900
3.900
3.900

```

3.900
3.900
3.900
3.900
3.900
3.900
0.000
0.000
0.000
0.057
0.368
0.679
0.990
1.260
1.260
1.300
1.300
1.342
1.342
1.381
1.527
1.598
1.754
1.779
1.955
1.981
1.987
2.000
2.000
2.000
2.000
2.014
2.162
2.270
2.526
2.782
3.000
3.673
3.700
4.644
4.700

```

```
> dos <- addDrug.Lexis(Sx, pdat, method = "dos", dpt = 6)
```

NOTE: timescale taken as 'per'

NOTE: end of exposure based on purchase and dosage (dpt).

```
> summary(dos)
```

Transitions:

To

From A D Records: Events: Risk time: Persons:

A 66 1 67 1 19 2

```
> dos
```

lex.id	per	age	lex.dur	lex.Cst	lex.Xst	F.ex	F.tf	F.ct	F.cd	G.ex	G.tf	G.ct
1	2006.00	56.00	0.20	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2006.20	56.20	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2006.80	56.80	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2007.40	57.40	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000

1	2008.00	58.00	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2008.60	58.60	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2009.20	59.20	0.43	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2009.63	59.63	0.17	A	A	FALSE	0.000	0.000	0.000	TRUE	0.000	0.000
1	2009.80	59.80	0.05	A	A	FALSE	0.000	0.000	0.000	TRUE	0.170	0.170
1	2009.85	59.85	0.55	A	A	FALSE	0.000	0.000	0.000	FALSE	0.217	0.217
1	2010.40	60.40	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.770	0.217
1	2011.00	61.00	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	1.370	0.217
1	2011.60	61.60	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	1.970	0.217
1	2012.20	62.20	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	2.570	0.217
1	2012.80	62.80	0.19	A	A	FALSE	0.000	0.000	0.000	FALSE	3.170	0.217
1	2012.99	62.99	0.03	A	A	FALSE	0.000	0.000	0.000	TRUE	3.357	0.217
1	2013.02	63.02	0.22	A	A	FALSE	0.000	0.000	0.000	TRUE	3.388	0.248
1	2013.23	63.23	0.17	A	A	FALSE	0.000	0.000	0.000	FALSE	3.605	0.465
1	2013.40	63.40	0.56	A	A	FALSE	0.000	0.000	0.000	FALSE	3.770	0.465
1	2013.96	63.96	0.00	A	A	TRUE	0.000	0.000	0.000	FALSE	4.334	0.465
1	2013.96	63.96	0.04	A	A	TRUE	0.000	0.000	0.000	FALSE	4.334	0.465
1	2014.00	64.00	0.25	A	A	TRUE	0.036	0.036	0.497	FALSE	4.370	0.465
1	2014.25	64.25	0.00	A	A	TRUE	0.286	0.286	4.000	FALSE	4.621	0.465
1	2014.25	64.25	0.26	A	A	TRUE	0.286	0.286	4.000	FALSE	4.621	0.465
1	2014.51	64.51	0.00	A	A	TRUE	0.545	0.545	8.000	FALSE	4.879	0.465
1	2014.51	64.51	0.09	A	A	TRUE	0.545	0.545	8.000	FALSE	4.879	0.465
1	2014.60	64.60	0.39	A	A	TRUE	0.636	0.636	8.567	FALSE	4.970	0.465
1	2014.99	64.99	0.00	A	A	TRUE	1.025	1.025	11.000	FALSE	5.360	0.465
1	2014.99	64.99	0.01	A	A	TRUE	1.025	1.025	11.000	FALSE	5.360	0.465
2	2008.00	57.00	0.10	A	A	TRUE	0.000	0.405	2.428	FALSE	0.000	0.000
2	2008.10	57.10	0.00	A	A	FALSE	0.095	0.500	3.000	FALSE	0.000	0.000
2	2008.10	57.10	0.50	A	A	FALSE	0.095	0.500	3.000	FALSE	0.000	0.000
2	2008.60	57.60	0.49	A	A	FALSE	0.600	0.500	3.000	FALSE	0.000	0.000
2	2009.09	58.09	0.11	A	A	FALSE	1.089	0.500	3.000	TRUE	0.000	0.000
2	2009.20	58.20	0.11	A	A	FALSE	1.200	0.500	3.000	TRUE	0.111	0.111
2	2009.31	58.31	0.49	A	A	FALSE	1.306	0.500	3.000	FALSE	0.217	0.217
2	2009.80	58.80	0.60	A	A	FALSE	1.800	0.500	3.000	FALSE	0.711	0.217
2	2010.40	59.40	0.60	A	A	FALSE	2.400	0.500	3.000	FALSE	1.311	0.217
2	2011.00	60.00	0.60	A	A	FALSE	3.000	0.500	3.000	FALSE	1.911	0.217
2	2011.60	60.60	0.00	A	A	FALSE	3.599	0.500	3.000	TRUE	2.510	0.217
2	2011.60	60.60	0.11	A	A	FALSE	3.600	0.500	3.000	TRUE	2.511	0.217
2	2011.71	60.71	0.01	A	A	TRUE	3.710	0.500	3.000	TRUE	2.621	0.328
2	2011.72	60.72	0.10	A	A	TRUE	3.716	0.506	3.216	FALSE	2.627	0.333
2	2011.81	60.81	0.39	A	A	TRUE	3.812	0.602	7.000	FALSE	2.723	0.333
2	2012.20	61.20	0.11	A	A	TRUE	4.200	0.990	9.326	FALSE	3.111	0.333
2	2012.31	61.31	0.49	A	A	FALSE	4.312	1.102	10.000	FALSE	3.223	0.333
2	2012.80	61.80	0.07	A	A	FALSE	4.800	1.102	10.000	FALSE	3.711	0.333
2	2012.87	61.87	0.33	A	A	TRUE	4.865	1.102	10.000	FALSE	3.776	0.333
2	2013.20	62.20	0.13	A	A	FALSE	5.199	1.435	12.000	FALSE	4.109	0.333
2	2013.33	62.33	0.07	A	A	TRUE	5.331	1.435	12.000	FALSE	4.242	0.333
2	2013.40	62.40	0.02	A	A	TRUE	5.400	1.504	13.606	FALSE	4.311	0.333
2	2013.42	62.42	0.33	A	A	TRUE	5.417	1.521	14.000	FALSE	4.328	0.333
2	2013.75	62.75	0.18	A	A	FALSE	5.750	1.855	16.000	FALSE	4.661	0.333
2	2013.93	62.93	0.07	A	A	TRUE	5.932	1.855	16.000	FALSE	4.843	0.333
2	2014.00	63.00	0.27	A	A	TRUE	6.000	1.923	16.409	FALSE	4.911	0.333
2	2014.27	63.27	0.30	A	A	FALSE	6.265	2.188	18.000	FALSE	5.176	0.333
2	2014.57	63.57	0.03	A	A	FALSE	6.566	2.188	18.000	TRUE	5.477	0.333
2	2014.60	63.60	0.13	A	A	FALSE	6.600	2.188	18.000	TRUE	5.511	0.367
2	2014.73	63.73	0.47	A	A	FALSE	6.733	2.188	18.000	FALSE	5.644	0.500
2	2015.20	64.20	0.60	A	A	FALSE	7.200	2.188	18.000	FALSE	6.111	0.500
2	2015.80	64.80	0.60	A	A	FALSE	7.800	2.188	18.000	FALSE	6.711	0.500

[illegible]

2.000
2.000
2.000
2.000
2.000
2.000
2.000
2.000
2.201
3.000
3.000
3.000
3.000
3.000
3.673
3.700
4.700
4.700

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

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:

```
      To
From  A D  Records:  Events: Risk time:  Persons:
      A 63 1       64       1       19       2
```

```
> fix
```

lex.id	per	age	lex.dur	lex.Cst	lex.Xst	F.ex	F.tf	F.ct	F.cd	G.ex	G.tf	G.ct
1	2006.00	56.00	0.20	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2006.20	56.20	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2006.80	56.80	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2007.40	57.40	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2008.00	58.00	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2008.60	58.60	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2009.20	59.20	0.43	A	A	FALSE	0.000	0.000	0.000	FALSE	0.000	0.000
1	2009.63	59.63	0.17	A	A	FALSE	0.000	0.000	0.000	TRUE	0.000	0.000
1	2009.80	59.80	0.60	A	A	FALSE	0.000	0.000	0.000	TRUE	0.170	0.170
1	2010.40	60.40	0.23	A	A	FALSE	0.000	0.000	0.000	TRUE	0.770	0.770
1	2010.63	60.63	0.37	A	A	FALSE	0.000	0.000	0.000	FALSE	1.000	1.000
1	2011.00	61.00	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	1.370	1.000
1	2011.60	61.60	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	1.970	1.000
1	2012.20	62.20	0.60	A	A	FALSE	0.000	0.000	0.000	FALSE	2.570	1.000
1	2012.80	62.80	0.19	A	A	FALSE	0.000	0.000	0.000	FALSE	3.170	1.000
1	2012.99	62.99	0.03	A	A	FALSE	0.000	0.000	0.000	TRUE	3.357	1.000
1	2013.02	63.02	0.38	A	A	FALSE	0.000	0.000	0.000	TRUE	3.388	1.031
1	2013.40	63.40	0.56	A	A	FALSE	0.000	0.000	0.000	TRUE	3.770	1.413
1	2013.96	63.96	0.00	A	A	TRUE	0.000	0.000	0.000	TRUE	4.334	1.978
1	2013.96	63.96	0.04	A	A	TRUE	0.000	0.000	0.000	TRUE	4.334	1.978
1	2014.00	64.00	0.02	A	A	TRUE	0.036	0.036	0.497	TRUE	4.370	2.013
1	2014.02	64.02	0.23	A	A	TRUE	0.054	0.054	0.752	FALSE	4.388	2.031
1	2014.25	64.25	0.00	A	A	TRUE	0.286	0.286	4.000	FALSE	4.621	2.031
1	2014.25	64.25	0.26	A	A	TRUE	0.286	0.286	4.000	FALSE	4.621	2.031
1	2014.51	64.51	0.00	A	A	TRUE	0.545	0.545	8.000	FALSE	4.879	2.031
1	2014.51	64.51	0.09	A	A	TRUE	0.545	0.545	8.000	FALSE	4.879	2.031
1	2014.60	64.60	0.39	A	A	TRUE	0.636	0.636	8.567	FALSE	4.970	2.031

1	2014.99	64.99	0.00	A	A	TRUE	1.025	1.025	11.000	FALSE	5.360	2.031
1	2014.99	64.99	0.01	A	A	TRUE	1.025	1.025	11.000	FALSE	5.360	2.031
2	2008.00	57.00	0.60	A	A	TRUE	0.000	0.405	1.214	FALSE	0.000	0.000
2	2008.60	57.60	0.00	A	A	FALSE	0.595	1.000	3.000	FALSE	0.000	0.000
2	2008.60	57.60	0.00	A	A	FALSE	0.595	1.000	3.000	FALSE	0.000	0.000
2	2008.60	57.60	0.49	A	A	FALSE	0.600	1.000	3.000	FALSE	0.000	0.000
2	2009.09	58.09	0.11	A	A	FALSE	1.089	1.000	3.000	TRUE	0.000	0.000
2	2009.20	58.20	0.60	A	A	FALSE	1.200	1.000	3.000	TRUE	0.111	0.111
2	2009.80	58.80	0.29	A	A	FALSE	1.800	1.000	3.000	TRUE	0.711	0.711
2	2010.09	59.09	0.31	A	A	FALSE	2.089	1.000	3.000	FALSE	1.000	1.000
2	2010.40	59.40	0.60	A	A	FALSE	2.400	1.000	3.000	FALSE	1.311	1.000
2	2011.00	60.00	0.60	A	A	FALSE	3.000	1.000	3.000	FALSE	1.911	1.000
2	2011.60	60.60	0.00	A	A	FALSE	3.599	1.000	3.000	TRUE	2.510	1.000
2	2011.60	60.60	0.11	A	A	FALSE	3.600	1.000	3.000	TRUE	2.511	1.001
2	2011.71	60.71	0.10	A	A	TRUE	3.710	1.000	3.000	TRUE	2.621	1.111
2	2011.81	60.81	0.39	A	A	TRUE	3.812	1.102	7.000	TRUE	2.723	1.213
2	2012.20	61.20	0.40	A	A	TRUE	4.200	1.490	8.163	TRUE	3.111	1.601
2	2012.60	61.60	0.20	A	A	TRUE	4.599	1.889	9.361	FALSE	3.510	2.000
2	2012.80	61.80	0.01	A	A	TRUE	4.800	2.090	9.963	FALSE	3.711	2.000
2	2012.81	61.81	0.05	A	A	FALSE	4.812	2.102	10.000	FALSE	3.723	2.000
2	2012.87	61.87	0.47	A	A	TRUE	4.865	2.102	10.000	FALSE	3.776	2.000
2	2013.33	62.33	0.07	A	A	TRUE	5.331	2.568	12.000	FALSE	4.242	2.000
2	2013.40	62.40	0.02	A	A	TRUE	5.400	2.637	13.606	FALSE	4.311	2.000
2	2013.42	62.42	0.51	A	A	TRUE	5.417	2.654	14.000	FALSE	4.328	2.000
2	2013.93	62.93	0.07	A	A	TRUE	5.932	3.168	16.000	FALSE	4.843	2.000
2	2014.00	63.00	0.57	A	A	TRUE	6.000	3.237	16.136	FALSE	4.911	2.000
2	2014.57	63.57	0.03	A	A	TRUE	6.566	3.803	17.269	TRUE	5.477	2.000
2	2014.60	63.60	0.33	A	A	TRUE	6.600	3.837	17.336	TRUE	5.511	2.034
2	2014.93	63.93	0.27	A	A	FALSE	6.932	4.168	18.000	TRUE	5.843	2.365
2	2015.20	64.20	0.37	A	A	FALSE	7.200	4.168	18.000	TRUE	6.111	2.634
2	2015.57	64.57	0.23	A	A	FALSE	7.566	4.168	18.000	FALSE	6.477	3.000
2	2015.80	64.80	0.60	A	A	FALSE	7.800	4.168	18.000	FALSE	6.711	3.000
2	2016.40	65.40	0.51	A	A	FALSE	8.400	4.168	18.000	FALSE	7.311	3.000
2	2016.91	65.91	0.09	A	A	FALSE	8.912	4.168	18.000	TRUE	7.822	3.000
2	2017.00	66.00	0.00	A	A	FALSE	9.000	4.168	18.000	TRUE	7.911	3.088
2	2017.00	66.00	0.60	A	A	FALSE	9.004	4.168	18.000	TRUE	7.914	3.092
2												

```
3.830
3.876
3.900
3.900
3.900
3.900
3.900
3.900
3.900
3.900
3.900
0.000
0.000
0.000
0.000
0.000
0.144
0.924
1.300
1.300
1.300
1.300
1.301
1.378
1.449
1.721
2.000
2.000
2.000
2.000
2.000
2.000
2.000
2.000
2.000
2.000
2.000
2.034
2.365
2.634
3.000
3.000
3.000
3.000
3.673
3.700
4.299
```

3.2 A more realistic example with timing

3.2.1 Follow-up data: DMlate

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

```
> data(DMlate) ; str(DMlate)
'data.frame':      10000 obs. of  7 variables:
 $ 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 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)

NOTE: entry.status has been set to "DM" for all.
NOTE: Dropping 4 rows with duration of follow up < tol

> summary(Lx)
```



```

'data.frame':      100736 obs. of  4 variables:
 $ lex.id: int  1 1 1 1 1 1 1 1 1 1 ...
 $ per   : num  1999 1999 1999 2000 2000 ...
 $ amt   : num  200 160 190 90 160 90 100 90 90 190 ...
 $ dpt   : num  1000 960 1330 360 640 630 500 450 630 950 ...

> 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)))
  1    2    3    4    5    6    7    8    9   10   11   12   13   14   15 Sum
374 418 414 406 391 383 361 429 375 415 394 401 375 394 223 5753
> str(purB)
'data.frame':      44695 obs. of  4 variables:
 $ lex.id: int  1 1 1 1 1 1 1 1 1 1 ...
 $ per   : num  1998 1998 1999 1999 2000 ...
 $ amt   : num  100 190 110 140 120 90 140 70 150 180 ...
 $ dpt   : num  800 1520 770 980 960 810 1260 560 1050 1440 ...

> 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)))
  1    2    3    4    5    6    7    8    9   10   11   12   13   14   15 Sum
374 418 414 406 391 383 361 429 375 415 394 401 375 394 223 5753
> str(purC)
'data.frame':      42302 obs. of  4 variables:
 $ lex.id: int  1 1 1 1 1 5 5 5 5 5 ...
 $ per   : num  1998 2000 2003 2007 2008 ...
 $ amt   : num  90 40 200 100 100 160 60 90 170 60 ...
 $ dpt   : num  450 240 1200 600 700 1120 360 630 1190 360 ...

> head(purC)
  lex.id    per amt  dpt
1      1 1998.363  90  450
2      1 2000.059  40  240
3      1 2002.642 200 1200
4      1 2006.568 100  600
5      1 2007.684 100  700
6      5 2008.775 160 1120

```

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

1000 and 500 persons

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

```
> Sx1 <- subset(Sx, lex.id < 1000)
> pur <- list(A = subset(purA, lex.id < 1000),
+           B = subset(purB, lex.id < 1000),
+           C = subset(purC, lex.id < 1000))
> system.time(ad1 <- addDrug.Lexis(Sx1, pur, tnam = "per", grace = 1/4))
```

Values of grace has been recycled across 3 drugs

NOTE: end of exposure based on differences in purchase times (per)
and amount purchased (amt).

	user	system	elapsed
	36.566	0.012	36.579

```
> summary(Sx1)
```

Transitions:

To

From	DM	Dead	Records:	Events:	Risk time:	Persons:
DM	6037	241	6278	241	5303.26	999

```
> summary(ad1)
```

Transitions:

To

From	DM	Dead	Records:	Events:	Risk time:	Persons:
DM	28720	241	28961	241	5303.26	999

We then cut the number of persons in half:

```
> Sx2 <- 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).

	user	system	elapsed
	18.696	0.000	18.693

```
> summary(Sx2)
```

Transitions:

To

From	DM	Dead	Records:	Events:	Risk time:	Persons:
DM	3023	118	3141	118	2653.65	499

```
> summary(ad2)
```

Transitions:

To

From	DM	Dead	Records:	Events:	Risk time:	Persons:
DM	15413	118	15531	118	2653.65	499

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

Fewer prescription records

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

```
> pur <- list(A = subset(purA, lex.id < 500 & runif(nrow(purA)) < 0.5),
+           B = subset(purB, lex.id < 500 & runif(nrow(purB)) < 0.5),
+           C = subset(purC, lex.id < 500 & runif(nrow(purC)) < 0.5))
> sapply(pur, nrow)
      A      B      C
2557 1098 1063
```

```
> system.time(ad3 <- 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).

```
      user  system elapsed
9.279    0.004    9.284
```

```
> summary(Sx2)
```

Transitions:

```
      To
From  DM Dead Records: Events: Risk time: Persons:
DM 3023 118      3141      118    2653.65      499
```

```
> summary(ad3)
```

Transitions:

```
      To
From  DM Dead Records: Events: Risk time: Persons:
DM 9646 118      9764      118    2653.65      499
```

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 < 500),
+           C = subset(purC, lex.id < 500))
> sapply(pur, nrow)
```

```
      B      C
2197 2170
```

```
> system.time(ad4 <- addDrug.Lexis(Sx2, 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).

```
      user  system elapsed
7.793    0.000    7.795
```

```
> summary(Sx2)
```

```

Transitions:
  To
From   DM Dead  Records:  Events: Risk time:  Persons:
  DM 3023  118      3141      118    2653.65      499
> summary(ad4)
Transitions:
  To
From   DM Dead  Records:  Events: Risk time:  Persons:
  DM 8976  118      9094      118    2653.65      499

```

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 0.02848 0.10277 0.18312 0.25620 1.00000

```

Half are smaller than 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:
  To
From   DM Dead  Records:  Events: Risk time:  Persons:
  DM 28720  241      28961      241    5303.26      999
> summary(adc <- coarse.Lexis(ad1, lim = c(1/6,1/2)))
Transitions:
  To
From   DM Dead  Records:  Events: Risk time:  Persons:
  DM 14670  241      14911      241    5303.26      999
> summary(adc$lex.dur)
      Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.0000 0.2079 0.3048 0.3557 0.4406 1.0000

```

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 3023  118      3141      118    2653.65      499

> system.time(ad4 <- addDrug.Lexis(Sx2,
+                                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).
   user  system elapsed
  7.759   0.001   7.760

> summary(ad4)
Transitions:
  To
From  DM Dead  Records:  Events: Risk time:  Persons:
  DM 8976  118      9094      118    2653.65      499

> #
> ad5 <- coarse.Lexis(ad4,
+                     lim = c(1/4, 1/2))
> summary(ad5)
Transitions:
  To
From  DM Dead  Records:  Events: Risk time:  Persons:
  DM 5460  118      5578      118    2653.65      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:

```
> ad4$keep <- with(ad4, (B.ex & B.ct == 0) |
+                     (C.ex & C.ct == 0))
> ad6 <- coarse.Lexis(ad4,
+                     lim = c(1/4, 1/2),
+                     keep = ad4$keep)
> summary(ad6)
Transitions:
  To
From  DM Dead  Records:  Events: Risk time:  Persons:
  DM 5578  118      5696      118    2653.65      499
```

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.