Simulation of multistate models with multiple timescales: `simLexis` in the `Epi` package

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Chapter 1

Using `simLexis`

1.1 Technicalities

First we set some graphics parameters for convenience and load the packages needed:

```
> options(width = 90,
+         show.signif.stars = FALSE,
+         SweaveHooks=list(fig = function()
+                             par(mar = c(3, 3, 1, 1),
+                                 mgp = c(3, 1, 0) / 1.6,
+                                 las = 1,
+                                lend = "butt",
+                                 bty = "n")))
> library(Epi)
> library(popEpi)
> library(survival)
> clear()
```

```
     R   Epi   popEpi
 4.4.2  2.59   0.4.12
```

1.2 Introduction

This vignette explains the machinery behind simulation of life histories through multistate models implemented in `simLexis`. In `simLexis` transition rates are allowed to depend on multiple time scales, including timescales defined as time since entry to a particular state (duration). This therefore also covers the case where time *at* entry into a state is an explanatory variable for the rates, since time at entry is merely (current) time minus duration. Thus, the set-up here goes beyond Markov- and semi-Markov-models, and brings simulation based estimation of state-occupancy probabilities into the realm of realistic multistate models.

   The basic idea is to simulate a new `Lexis` object [3, 1] as defined in the `Epi` package for R, based on 1) a multistate model defined by its states and the transition rates between them and 2) an initial population of individuals.

   Thus the output will be a `Lexis` object describing the transitions of a predefined set of persons through a multistate model. Therefore, if persons are defined to be identical at

1

start, then calculation of the probability of being in a particular state at a given time boils down to a simple enumeration of the fraction of the persons in the particular state at the given time. Bar of course the (binomial) simulation error, but this can be brought down by simulation a sufficiently large number of persons.

An observed `Lexis` object with follow-up of persons through a number of states will normally be the basis for estimation of transition rates between states, and thus will contain all information about covariates determining the occurrence rates, in particular the *timescales* [2]. Hence, the natural input to simulation from an estimated multistate model will typically be an object of the same structure as the originally observed. Since transitions and times are what is simulated, any values of `lex.Xst` and `lex.dur` in the input object will of course be ignored.

This first chapter of this vignette shows by an example how to use the function `simLexis` and display the results. The second chapter discusses in more detail how the simulation machinery is implemented and is not needed for the practical use of `simLexis`.

1.3   `simLexis` in practice

This section is largely a commented walk-trough of the example from the help-page of `simLexis`, with a larger number of simulated persons in order to minimize the pure simulation variation.

When we want to simulate transition times through a multistate model where transition rates may depend on time since entry to the current or a previous state, it is essential that we have a machinery to keep track of the transition time on *all* time scales, as well as a mechanism that can initiate a new time scale to 0 when a transition occurs to a state where we shall use time since entry as determinant of exit rates from that state. This is provided by `simLexis`.

1.3.1   Input for the simulation

Input for simulation of a single trajectory through a multistate model requires a representation of the *current status* of a person; the starting conditions. The object that we supply to the simulation function must contain information about all covariates and all timescales upon which transitions depend, and in particular which one(s) of the timescales that are defined as time since entry into a particular state. Hence, starting conditions should be represented as a `Lexis` object (where `lex.dur` and `lex.Xst` are ignored, since there is no follow-up yet), where the time scale information is in the attributes `time.scales` and `time.since` respectively.

Note that `time.scales` attribute is a vector of names of variables in the `Lexis` object, so all of these variables should be present even if they are not used in the models for the transitions, and they should be set to 0; if they are not in the initial dataset, `simLexis` will crash, if they are `NA`, the `simLexis` will produce an object with 0 rows.

Thus there are two main arguments to a function to simulate from a multistate model:

1. A `Lexis` object representing the initial states and covariates of the population to be simulated. This has to have the same structure as the original `Lexis` object representing the multistate model from which transition rates in the model were

estimated. As noted above, the values for `lex.Xst` and `lex.dur` are not required (since these are the quantities that will be simulated).

2. A transition object, representing the transition intensities between states, which should be a list of lists of intensity representations. As an intensity representation we mean a function that for a given `Lexis` object can be used to produce estimates of the transition intensities at a set of supplied time points.

   The names of the elements of the transition object (which are lists) will be names of the *transient* states, that is the states *from* which a transition can occur. The names of the elements of each of these lists are the names of states *to* which transitions can occur (which may be either transient or absorbing states).

   Hence, if the transition object is called `Tr` then `TR$A$B` (or `Tr[["A"]][["B"]]`) will represent the transition intensity from state `A` to the state `B`.

   The entries in the transition object can be either `glm` objects (either with `poisson` or `poisreg` family), representing Poisson models for the transitions, `coxph` objects representing an intensity model along one time scale, or simply a function that takes a `Lexis` object as input and returns an estimated intensity for each row.

In addition to these two input items, there will be a couple of tuning parameters.

The output of the function will simply be a `Lexis` object with simulated transitions between states. This will be the basis for deriving sensible statistics from the `Lexis` object — see next section.

1.4   Setting up a `Lexis` object

As an example we will use the `DMlate` dataset from the `Epi` package; it is a dataset simulated to resemble a random sample of 10,000 patients from the Danish National Diabetes Register.

We start by loading the `Epi` package:

```
> options( width=90 )
> library( Epi )
> print( sessionInfo(), l=F )
R version 4.4.2 (2024-10-31 ucrt)
Platform: x86_64-w64-mingw32/x64
Running under: Windows 10 x64 (build 19045)

Matrix products: default


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

other attached packages:
[1] tidyr_1.3.1    dplyr_1.1.4    survival_3.7-0 popEpi_0.4.12  Epi_2.59

loaded via a namespace (and not attached):
 [1] etm_1.1.1          vctrs_0.6.5         nlme_3.1-166        cli_3.6.3
 [5] rlang_1.1.4        purrr_1.0.2         cmprsk_2.2-12       generics_0.1.3
 [9] data.table_1.16.2  zoo_1.8-12          glue_1.8.0          plyr_1.8.9
```

```
[13] fansi_1.0.6          grid_4.4.2         tibble_3.2.1      MASS_7.3-61
[17] numDeriv_2016.8-1.1 lifecycle_1.0.4    compiler_4.4.2    Rcpp_1.0.13-1
[21] pkgconfig_2.0.3     mgcv_1.9-1         lattice_0.22-6    R6_2.5.1
[25] tidyselect_1.2.1    utf8_1.2.4         pillar_1.9.0      parallel_4.4.2
[29] splines_4.4.2       magrittr_2.0.3     Matrix_1.7-1      withr_3.0.2
[33] tools_4.4.2
```

First we load the diabetes data and set up a simple illness-death model:

```
> data(DMlate)
> dml <- Lexis( entry = list(Per=dodm, Age=dodm-dobth, DMdur=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
```

This is just data for a simple survival model with states `DM` and `Dead`. Now we cut the follow-up at insulin start, which for the majority of patients (T2D) is a clinical indicator of deterioration of disease regulation. We therefore also introduce a new timescale, and split the non-precursor states, so that we can address the question of ever having been on insulin:

```
> dmi <- cutLexis( dml, cut = dml$doins,
+                       pre = "DM",
+                 new.state = "Ins",
+                 new.scale = "t.Ins",
+               split.states = TRUE )
> summary( dmi, timeScales=T )
Transitions:
     To
From    DM  Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM  6157 1694 2048         0      9899     3742   45885.49      9899
  Ins    0 1340    0       451      1791      451    8387.77      1791
  Sum 6157 3034 2048       451     11690     4193   54273.27      9996

Timescales:
  Per   Age DMdur t.Ins
   ""    ""    "" "Ins"
```

Note that we show the time scales in the `Lexis` object, and that it is indicated that the time scale `t.Ins` is defined as time since entry into stat state `Ins`.

  We can show how many person-years we have and show the number of transitions and transition rates (per 1000), using the `boxes.Lexis` function to display the states and the number of transitions between them:

```
> boxes( dmi, boxpos = list(x=c(20,20,80,80),
+                           y=c(80,20,80,20)),
+           scale.R = 1000, show.BE = TRUE )
```

1.5   Analysis of rates

In the `Lexis` object (which is just a data frame) each person is represented by one record for each transient state occupied, thus in this case either 1 or 2 records; those who have a recorded time both without and with insulin have two records.
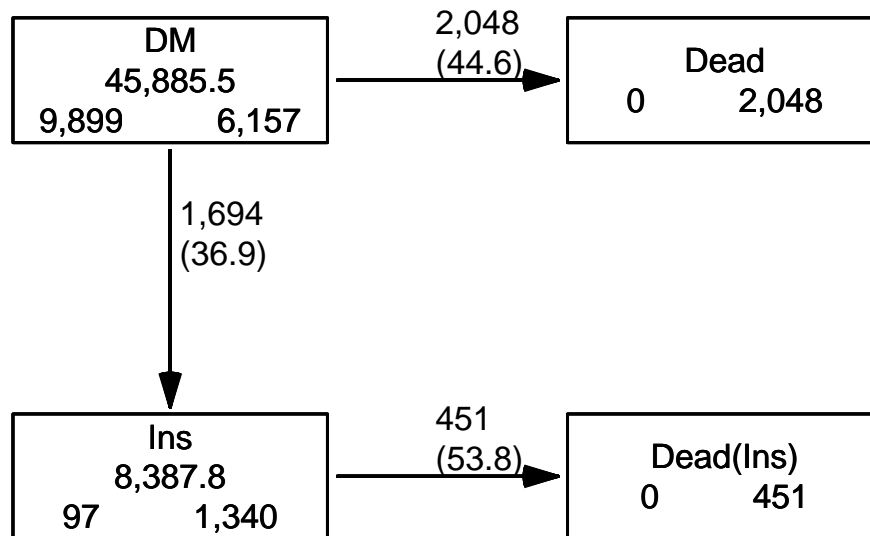
Figure 1.1: *Data overview for the* `dmi` *dataset. Numbers in the boxes are person-years and the number of persons who begin, resp. end their follow-up in each state, and numbers on the arrows are no. of transitions and rates (transition intensities) per 1000 PY..*/`simLexis-boxes`

In order to be able to fit Poisson models with occurrence rates varying by the different time-scales, we split the follow-up in 3-month intervals for modeling:

```
> Si <- splitLexis( dmi, seq(0,20,1/4), "DMdur" )
> summary( Si )
Transitions:
     To
From       DM   Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM   184986  1694 2048         0    188728     3742   45885.49      9899
  Ins       0 34707    0       451     35158      451    8387.77      1791
  Sum  184986 36401 2048       451    223886     4193   54273.27      9996

> print( subset( Si, lex.id==97 )[,1:10], digits=6 )

 lex.id     Per    Age DMdur t.Ins lex.dur lex.Cst  lex.Xst sex   dobth
     97 1997.55 58.93  0.00    NA    0.25      DM       DM   F 1938.62
     97 1997.80 59.18  0.25    NA    0.25      DM       DM   F 1938.62
     97 1998.05 59.43  0.50    NA    0.25      DM       DM   F 1938.62
     97 1998.30 59.68  0.75    NA    0.25      DM       DM   F 1938.62
     97 1998.55 59.93  1.00    NA    0.25      DM       DM   F 1938.62
     97 1998.80 60.18  1.25    NA    0.25      DM       DM   F 1938.62
     97 1999.05 60.43  1.50    NA    0.25      DM       DM   F 1938.62
     97 1999.30 60.68  1.75    NA    0.25      DM       DM   F 1938.62
     97 1999.55 60.93  2.00    NA    0.18      DM      Ins   F 1938.62
     97 1999.72 61.11  2.18  0.00    0.07     Ins      Ins   F 1938.62
     97 1999.80 61.18  2.25  0.07    0.25     Ins      Ins   F 1938.62
     97 2000.05 61.43  2.50  0.32    0.25     Ins      Ins   F 1938.62
     97 2000.30 61.68  2.75  0.57    0.25     Ins      Ins   F 1938.62
     97 2000.55 61.93  3.00  0.82    0.01     Ins Dead(Ins)  F 1938.62
```

Note that when we split the follow-up, each person's follow up now consists of many records, each with the *current* values of the timescales at the start of the interval represented by the record. In the modeling we shall assume that the rates are constant within each 6-month interval, but the *size* of these rates we model as smooth functions of the time scales (that is the values at the beginning of each interval).

The approach often used in epidemiology where one parameter is attached to each interval of time (or age) is not feasible when more than one time scale is used, because intervals are not classified the same way on all timescales.

We shall use natural splines (restricted cubic splines) for the analysis of rates, and hence we must allocate knots for the splines. This is done for each of the time-scales, and separately for the transition out of states `DM` and `Ins`. For age, we place the knots so that the number of events is the same between each pair of knots, but only half of this beyond each of the boundary knots, whereas for the timescales `DMdur` and `tIns` where we have observation from a well-defined 0, we put knots at 0 and place the remaining knots so that the number of events is the same between each pair of knots as well as outside the boundary knots.

```
> nk <- 5
> ( ai.kn <- with( subset(Si,lex.Xst=="Ins" & lex.Cst!=lex.Xst ),
+                  quantile( Age+lex.dur  , probs=(1:nk-0.5)/nk ) ) )
     10%       30%       50%       70%       90%
23.23751 48.82218 58.63244 67.79028 78.88542
> ( ad.kn <- with( subset(Si,lex.Xst=="Dead"),
+                  quantile( Age+lex.dur  , probs=(1:nk-0.5)/nk ) ) )
     10%       30%       50%       70%       90%
61.91951 72.52731 78.43121 83.32348 90.15195
> ( di.kn <- with( subset(Si,lex.Xst=="Ins" & lex.Cst!=lex.Xst ),
+                  c(0,quantile( DMdur+lex.dur, probs=(1:(nk-1))/nk ) )) )
                   20%        40%        60%        80%
0.00000000 0.06570842 0.45448323 3.28761123 6.63764545
> ( dd.kn <- with( subset(Si,lex.Xst=="Dead"),
+                  c(0,quantile( DMdur+lex.dur, probs=(1:(nk-1))/nk ) )) )
                 20%       40%       60%       80%
0.0000000 0.7687885 2.1327858 4.0465435 6.5232033
> ( ti.kn <- with( subset(Si,lex.Xst=="Dead(Ins)"),
+                  c(0,quantile( t.Ins+lex.dur, probs=(1:(nk-1))/nk ) )) )
                 20%       40%       60%       80%
0.0000000 0.3093771 1.1307324 2.5489391 4.9117043
```

Note that when we tease out the event records for transition to *transient* states (in this case `Ins`, that is `lex.Xst=="Ins"`), we should add `lex.Cst!=lex.Xst`, to include only transition records and avoiding including records of sojourn time in the transient state.

We then fit Poisson models to transition rates, using the wrapper `Ns` from the `Epi` package to simplify the specification of the rates:

```
> library( splines )
> DM.Ins <- glm( (lex.Xst=="Ins") ~ Ns( Age  , knots=ai.kn ) +
+                                    Ns( DMdur, knots=di.kn ) +
+                                    I(Per-2000) + sex,
+               family=poisson, offset=log(lex.dur),
+               data = subset(Si,lex.Cst=="DM") )
> ci.exp( DM.Ins )
```

```
                              exp(Est.)        2.5%       97.5%
(Intercept)                  1.37516629 1.21414923 1.55753699
Ns(Age, knots = ai.kn)1       0.23411761 0.19185266 0.28569349
Ns(Age, knots = ai.kn)2       0.23166177 0.19576557 0.27414000
Ns(Age, knots = ai.kn)3       0.02835009 0.02284379 0.03518363
Ns(Age, knots = ai.kn)4       0.38067392 0.32945713 0.43985278
Ns(DMdur, knots = di.kn)1   0.04462626 0.03373451 0.05903459
Ns(DMdur, knots = di.kn)2   0.22388988 0.19028663 0.26342723
Ns(DMdur, knots = di.kn)3   0.03379141 0.02574708 0.04434907
Ns(DMdur, knots = di.kn)4   0.47100646 0.40783317 0.54396529
I(Per - 2000)                0.97381513 0.96082049 0.98698552
sexF                         0.73757407 0.66886782 0.81333785
> class( DM.Ins )
[1] "glm" "lm"
```

We can also fit this model with a slightly simpler syntax using the `glm.Lexis` function:

```
> DM.Ins <- glm.Lexis( Si, from = "DM", to = "Ins",
+                      formula = ~ Ns( Age  , knots=ai.kn ) +
+                                  Ns( DMdur, knots=di.kn ) +
+                                  I(Per-2000) + sex )
stats::glm Poisson analysis of Lexis object Si with log link:
Rates for the transition:
DM->Ins
> ci.exp( DM.Ins )
                              exp(Est.)        2.5%       97.5%
(Intercept)                  1.37516630 1.21415038 1.55753552
Ns(Age, knots = ai.kn)1       0.23411761 0.19185214 0.28569426
Ns(Age, knots = ai.kn)2       0.23166177 0.19576473 0.27414118
Ns(Age, knots = ai.kn)3       0.02835009 0.02284374 0.03518371
Ns(Age, knots = ai.kn)4       0.38067392 0.32945601 0.43985427
Ns(DMdur, knots = di.kn)1   0.04462625 0.03373347 0.05903639
Ns(DMdur, knots = di.kn)2   0.22388988 0.19028599 0.26342813
Ns(DMdur, knots = di.kn)3   0.03379141 0.02574705 0.04434912
Ns(DMdur, knots = di.kn)4   0.47100646 0.40783201 0.54396683
I(Per - 2000)                0.97381513 0.96082027 0.98698574
sexF                         0.73757407 0.66886641 0.81333956
> class( DM.Ins )
[1] "glm.lex" "glm"      "lm"
```

So we have a slightly simpler syntax, and we get an informative message of which transition(s) we are modeling. However we do not have `update` method for these objects.

```
> DM.Dead <- glm.Lexis( Si, from = "DM", to = "Dead",
+                      formula = ~ Ns( Age  , knots=ad.kn ) +
+                                  Ns( DMdur, knots=dd.kn ) +
+                                  I(Per-2000) + sex )
stats::glm Poisson analysis of Lexis object Si with log link:
Rates for the transition:
DM->Dead
> Ins.Dead <- glm.Lexis( Si, from = "Ins",
+                      formula = ~ Ns( Age  , knots=ad.kn ) +
+                                  Ns( DMdur, knots=dd.kn ) +
+                                  Ns( t.Ins, knots=ti.kn ) +
+                                  I(Per-2000) + sex )
```

```
stats::glm Poisson analysis of Lexis object Si with log link:
Rates for the transition:
Ins->Dead(Ins)
```

Note the similarity of the code used to fit the three models, is is mainly redefining the response variable (`to` state) and the subset of the data used (`from` state). Also note that the last model need no specification of `to`, the default is to model all transitions from the `from` state, and his case there is only one.

1.6   The mortality rates

This section discusses in some detail how to extract ad display the mortality rates from the models fitted. But it is not necessary for understanding how to use `simLexis` in practice.

1.6.1   Proportionality of mortality rates

Note that we have fitted separate models for the three transitions, there is no assumption of proportionality between the mortality rates from `DM` and `Ins`.

However, there is nothing that prevents us from testing this assumption; we can just fit a model for the mortality rates in the entire data frame `Si`, and compare the deviance from this with the sum of the deviances from the separate models using the `glm.Lexis` function:

```
> All.Dead <- glm.Lexis( Si, to = c("Dead(Ins)","Dead"),
+                     formula = ~ Ns( Age  , knots=ad.kn ) +
+                                 Ns( DMdur, knots=dd.kn ) +
+                                 lex.Cst +
+                                 I(Per-2000) + sex )
stats::glm Poisson analysis of Lexis object Si with log link:
Rates for transitions:
Ins->Dead(Ins)
DM->Dead
> round( ci.exp( All.Dead ), 3 )
```

	exp(Est.)	2.5%	97.5%
(Intercept)	0.057	0.049	0.065
Ns(Age, knots = ad.kn)1	4.101	3.462	4.858
Ns(Age, knots = ad.kn)2	4.661	4.064	5.346
Ns(Age, knots = ad.kn)3	15.434	13.548	17.583
Ns(Age, knots = ad.kn)4	7.509	6.695	8.421
Ns(DMdur, knots = dd.kn)1	0.466	0.384	0.565
Ns(DMdur, knots = dd.kn)2	0.642	0.563	0.731
Ns(DMdur, knots = dd.kn)3	0.229	0.165	0.318
Ns(DMdur, knots = dd.kn)4	0.796	0.713	0.888
lex.CstIns	2.168	1.947	2.415
I(Per - 2000)	0.965	0.954	0.977
sexF	0.665	0.614	0.721

Incidentally we could have dispensed with the `to=` argument too, because the default is to take `to` to be all absorbing states in the model.

From the parameter values we would in a simple setting just claim that start of insulin-treatment was associated with a slightly more than doubling of mortality.

The model `All.dead` assumes that the age- and DM-duration effects on mortality in the `DM` and `Ins` states are the same, and moreover that there is no effect of insulin duration, but merely a mortality that is larger by a multiplicative constant not depending on insulin duration. The model `DM.Dead` has 8 parameters to describe the dependency on age and DM duration, the model `Ins.Dead` has 12 for the same plus the insulin duration (a natural spline with k knots gives $k - 1$ parameters, and we chose $k = 5$ above).

We can compare the fit of the simple proportional hazards model with the fit of the separate models for the two mortality rates, by adding up the deviances and d.f. from these:

```
> what <- c("null.deviance","df.null","deviance","df.residual")
> ( rD <- unlist(  DM.Dead[what] ) )
null.deviance        df.null       deviance    df.residual
    22535.77      188727.00      20412.81      188717.00
> ( rI <- unlist( Ins.Dead[what] ) )
null.deviance        df.null       deviance    df.residual
    4867.127      35157.000      4211.735      35143.000
> ( rA <- unlist( All.Dead[what] ) )
null.deviance        df.null       deviance    df.residual
    27415.21      223885.00      24705.70      223874.00
> round( c( dd <- rA-(rI+rD), "pVal"=1-pchisq(dd[3],dd[4]+1) ), 3 )
null.deviance        df.null       deviance    df.residual pVal.deviance
       12.314          1.000         81.154         14.000         0.000
```

Thus we see there is a substantial non-proportionality of mortality rates from the two states; but a test provides no clue whatsoever to the particular *shape* of the non-proportionality.

To this end, we shall explore the predicted mortalities under the two models quantitatively in more detail. Note that the reason that there is a difference in the null deviances (and a difference of 1 in the null d.f.) is that the null deviance of `All.Dead` refer to a model with a single intercept, that is a model with constant and *identical* mortality rates from the states `DM` and `Ins`, whereas the null models for `DM.Dead` and `Ins.Dead` have constant but *different* mortality rates from the states `DM` and `Ins`. This is however irrelevant for the comparison of the *residual* deviances.

1.6.2   How the mortality rates look

If we want to see how the mortality rates are modelled in `DM.Dead` and `Ins.Dead` in relation to `All.Dead`, we make a prediction of rates for say men diagnosed in different ages and going on insulin at different times after this. So we consider men diagnosed in ages 40, 50, 60 and 70, and who either never enter insulin treatment or do it 0, 2 or 5 years after diagnosis of DM.

To this end we create a prediction data frame where we have observation times from diagnosis and 12 years on (longer would not make sense as this is the extent of the data).

But we start by setting up an array to hold the predicted mortality rates, classified by diabetes duration, age at diabetes onset, time of insulin onset, and of course type of model. What we want to do is to plot the age-specific mortality rates for persons not on insulin, and for persons starting insulin at different times after DM. The mortality curves start at

the age where the person gets diabetes and continues 12 years; for persons on insulin they
start at the age when they initiate insulin.

```
> pr.rates <- NArray( list( DMdur = seq(0,12,0.1),
+                           DMage = 4:7*10,
+                           r.Ins = c(NA,0,2,5),
+                           model = c("DM/Ins","All"),
+                            what = c("rate","lo","hi") ) )
> str( pr.rates )
 logi [1:121, 1:4, 1:4, 1:2, 1:3] NA NA NA NA NA NA ...
 - attr(*, "dimnames")=List of 5
  ..$ DMdur: chr [1:121] "0" "0.1" "0.2" "0.3" ...
  ..$ DMage: chr [1:4] "40" "50" "60" "70"
  ..$ r.Ins: chr [1:4] NA "0" "2" "5"
  ..$ model: chr [1:2] "DM/Ins" "All"
  ..$ what : chr [1:3] "rate" "lo" "hi"
```

For convenience the `Epi` package contains a function that computes predicted (log-)rates
with c.i. — it is merely a wrapper for `predict.glm`.

So we set up the prediction data frame and modify it in loops over ages at onset and
insulin onset in order to collect the predicted rates in different scenarios:

```
> nd <- data.frame( DMdur = as.numeric( dimnames(pr.rates)[[1]] ),
+               lex.Cst = factor( 1, levels=1:4,
+                                 labels=levels(Si$lex.Cst) ),
+                   sex = factor( 1, levels=1:2, labels=c("M","F")) )
```

Note that we did *not* insert `lex.dur` as covariate in the prediction frame. This would be
required if we used the `poisson` family with the `glm`, but the wrapper `glm.Lexis` uses the
`poisreg` family, so `lex.dur` is ignored and predictions always comes in the (inverse) units
of `lex.dur`. So we get rates per 1 person-year in the predictions.

```
> for( ia in dimnames(pr.rates)[[2]] )
+     {
+ dnew <- transform( nd, Age = as.numeric(ia)+DMdur,
+                         Per = 1998+DMdur )
+ pr.rates[,ia,1,"DM/Ins",] <- ci.pred(  DM.Dead, newdata = dnew )
+ pr.rates[,ia,1,"All"   ,] <- ci.pred( All.Dead, newdata = dnew )
+ for( ii in dimnames(pr.rates)[[3]][-1] )
+     {
+ dnew = transform( dnew, lex.Cst = factor( 2, levels=1:4,
+                                 labels=levels(Si$lex.Cst) ),
+                         t.Ins = ifelse( (DMdur-as.numeric(ii)) >= 0,
+                                          DMdur-as.numeric(ii), NA ) )
+ pr.rates[,ia, ii ,"DM/Ins",] <- ci.pred( Ins.Dead, newdata = dnew )
+ pr.rates[,ia, ii ,"All"   ,] <- ci.pred( All.Dead, newdata = dnew )
+     }
+     }
```

So for each age at DM onset we make a plot of the mortality as function of current age
both for those with no insulin treatment and those that start insulin treatment 0, 2 and 5
years after diabetes diagnosis, thus 4 curves (with c.i.). These curves are replicated with a
different color for the simplified model.

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, las=1 )
> plot( NA, xlim=c(40,82), ylim=c(5,300), bty="n",
+       log="y", xlab="Age", ylab="Mortality rate per 1000 PY" )
> abline( v=seq(40,80,5), h=outer(1:9,10^(0:2),"*"), col=gray(0.8) )
> for( aa in 4:7*10 ) for( ii in 1:4 )
+    matshade( aa+as.numeric(dimnames(pr.rates)[[1]]),
+              cbind( pr.rates[,paste(aa),ii,"DM/Ins",],
+                     pr.rates[,paste(aa),ii,"All"   ,] )*1000,
+              type="l", lty=1, lwd=2,
+              col=c("red","limegreen") )
```
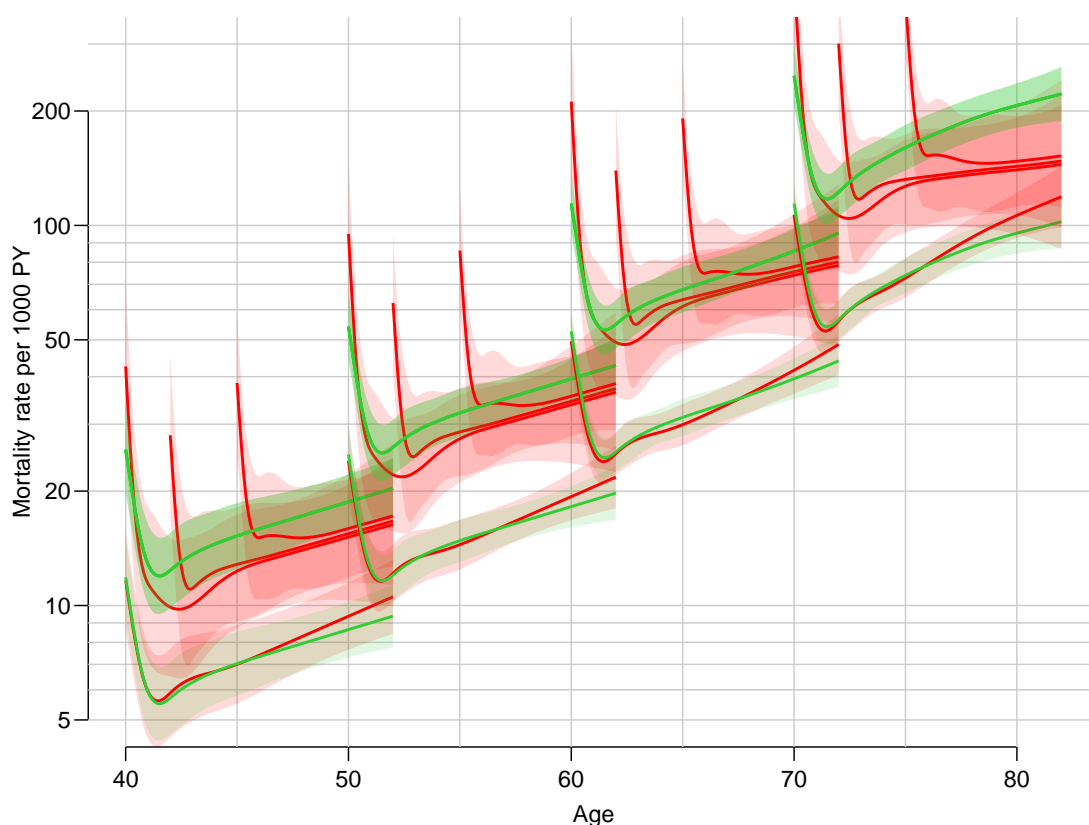

Figure 1.2: *Estimated mortality rates for male diabetes patients with no insulin (lower sets of curves) and insulin (upper curves), with DM onset in age 40, 50, 60 and 70. The red curves are from the models with separate age effects for persons with and without insulin, and a separate effect of insulin duration. The green curves are from the model with common age-effects and only a time-dependent effect of insulin, assuming no effect of insulin duration (the classical time-dependent variable approach). Hence the upper green curve is common for any time of insulin inception.*   `./simLexis-mort-int`

From figure 1.2 we see that there is a substantial insulin-duration effect which is not accommodated by the simple model with only one time-dependent variable to describe the insulin effect. Note that the simple model (green curves) for those on insulin does not depend in insulin duration, and hence the mortality curves for those on insulin are just parallel to the mortality curves for those not on insulin, regardless of diabetes duration (or age) at the time of insulin initiation. This is the proportional hazards assumption. Thus

the effect of insulin initiation is under-estimated for short duration of insulin and over-estimated for long duration of insulin.

This is the major discrepancy between the two models, and illustrates the importance of being able to accommodate different time scales, but there is also a declining overall insulin effect by age which is not accommodated by the proportional hazards approach.

Finally, this plot illustrates an important feature in reporting models with multiple timescales; all timescales must be represented in the predicted rates, only reporting the effect of one timescale, conditional on a fixed value of other timescales is misleading since all timescales by definition advance at the same pace. For example, the age-effect for a fixed value of insulin duration really is a misnomer since it does not correspond to any real person's follow-up, but to the mortality of persons in different ages but with the same duration of insulin use.

1.7   Input to the `simLexis` function

We want to estimate the cumulative probability of being in each of the 4 states, so that we can assess the fraction of diabetes pateints that go on insulin

In order to simulate from the multistate model with the estimated transition rates, and get the follow-up of a hypothetical cohort, we must supply *both* the transition rates and the structure of the model *as well as* the initial cohort status to `simLexis`.

1.7.1   The transition object

We first put the models into an object representing the transitions; note this is a list of lists, the latter having `glm` objects as elements:

```
> Tr <- list( "DM" = list( "Ins"      = DM.Ins,
+                          "Dead"     = DM.Dead  ),
+             "Ins" = list( "Dead(Ins)" = Ins.Dead ) )
```

Now we have the description of the rates and of the structure of the model. The `Tr` object defines the states and models for all transitions between them; the object `Tr$A$B` is the model for the transition intensity from state `A` to state `B`.

1.7.2   The initial cohort

We now define an initial `Lexis` object of persons with all relevant covariates defined. Note that we use `NULL` as row indicator in the `Lexis` object we used for modeling; this conserves the `time.scale` and `time.since` attributes which are needed for the simulation:

```
> str( ini <- Si[NULL,1:9] )
Classes 'Lexis' and 'data.frame':       0 obs. of  9 variables:
 $ lex.id : int
 $ Per    : num
 $ Age    : num
 $ DMdur  : num
 $ t.Ins  : num
 $ lex.dur: num
 $ lex.Cst: Factor w/ 4 levels "DM","Ins","Dead",..:
 $ lex.Xst: Factor w/ 4 levels "DM","Ins","Dead",..:
```

```
$ sex    : Factor w/ 2 levels "M","F":
- attr(*, "time.scales")= chr [1:4] "Per" "Age" "DMdur" "t.Ins"
- attr(*, "time.since")= chr [1:4] "" "" "" "Ins"
- attr(*, "breaks")=List of 4
 ..$ Per  : NULL
 ..$ Age  : NULL
 ..$ DMdur: num [1:81] 0 0.25 0.5 0.75 1 1.25 1.5 1.75 2 2.25 ...
 ..$ t.Ins: NULL
```

We now have an empty `Lexis` object with attributes reflecting the timescales in the multistate model we want to simulate from. But we must enter some data to represent the initial state of the persons whose follow-up we want to simulate through the model; so fill in data for one man and one woman:

```
> ini[1:2,"lex.id"] <- 1:2
> ini[1:2,"lex.Cst"] <- "DM"
> ini[1:2,"Per"] <- 1995
> ini[1:2,"Age"] <- 60
> ini[1:2,"DMdur"] <- 5
> ini[1:2,"sex"] <- c("M","F")
> ini
 lex.id  Per Age DMdur t.Ins lex.dur lex.Cst lex.Xst sex
      1 1995  60     5    NA      NA      DM    <NA>   M
      2 1995  60     5    NA      NA      DM    <NA>   F
```

So the persons starts in age 60 in 1995 with 5 years of diabetes duration. Note that the `t.Ins` is `NA`, because this is a timescale that first comes alive if a transtion to `Ins` is simulated.

1.8   Simulation of the follow-up

Now we simulate life-courses of a 1000 of each of these persons using the estimated model. The `t.range` argument gives the times range where the integrated intensities (cumulative rates) are evaluated and where linear interpolation is used when simulating transition times. Note that this must be given in the same units as `lex.dur` in the `Lexis` object used for fitting the models for the transitions. It is not a parameter that can be easily determined from the `TR` object, hence it must be supplied by the user.

```
> set.seed(52381764)
> Nsim <- 500
> system.time( simL <- simLexis( Tr,
+                                 ini,
+                           t.range = 12,
+                                N = Nsim ) )
  bruger    system forløbet
    1.32      0.12     1.43
```

The result is a `Lexis` object — a data frame representing the simulated follow-up of 1000 persons (500 identical men and 500 identical women) according to the rates we estimated from the original dataset.

```
> summary( simL, by="sex" )
```

```
$M

Transitions:
     To
From   DM Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM  148 185  167         0       500      352    3697.59       500
  Ins   0 136    0        49       185       49    1023.96       185
  Sum 148 321  167        49       685      401    4721.55       500

$F

Transitions:
     To
From   DM Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM  214 183  103         0       500      286    4223.33       500
  Ins   0 144    0        39       183       39    1020.36       183
  Sum 214 327  103        39       683      325    5243.69       500
```

1.8.1   Using other models for simulation

Proportional hazards Poisson model

We fitted a proportional mortality model `All.Dead` (which fitted worse than the other two), this is a model for *both* the transition from `DM` to `Death` *and* from `Ins` to `Dead(Ins)`, assuming that they are proportional. But it can easily be used in the simulation set-up, because the state is embedded in the model via the term `lex.Cst`, which is updated during the simulation.

Simulation using this instead just requires that we supply a different transition object:

```
> Tr.p <- list( "DM" = list( "Ins"       = DM.Ins,
+                            "Dead"       = All.Dead ),
+               "Ins" = list( "Dead(Ins)" = All.Dead ) )
> system.time( simP <- simLexis( Tr.p,
+                                   ini,
+                                 t.range = 12,
+                                     N = Nsim ) )
  bruger    system forløbet
    1.36      0.15     1.50
> summary( simP, by="sex" )
$M

Transitions:
     To
From   DM Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM  148 222  130         0       500      352    3703.19       500
  Ins   0 127    0        95       222       95    1049.95       222
  Sum 148 349  130        95       722      447    4753.14       500

$F

Transitions:
     To
From   DM Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM  224 171  105         0       500      276    4323.34       500
```

```
  Ins    0 118    0          53         171         53      861.93         171
  Sum  224 289  105          53         671        329     5185.27         500
```

Proportional hazards Cox model

A third possibility would be to replace the two-time scale proportional mortality model by
a one-time-scale Cox-model, using diabetes duration as time scale, and age at diagnosis of
DM as (fixed) covariate:

```
> library( survival )
> Cox.Dead <- coxph( Surv( DMdur, DMdur+lex.dur,
+                          lex.Xst %in% c("Dead(Ins)","Dead")) ~
+                   Ns( Age-DMdur, knots=ad.kn ) +
+                   I(lex.Cst=="Ins") +
+                   I(Per-2000) + sex,
+              data = Si )
> round( ci.exp( Cox.Dead ), 3 )
                                 exp(Est.)   2.5%   97.5%
Ns(Age - DMdur, knots = ad.kn)1      4.172  3.535   4.923
Ns(Age - DMdur, knots = ad.kn)2      4.502  3.824   5.301
Ns(Age - DMdur, knots = ad.kn)3     16.077 14.087  18.348
Ns(Age - DMdur, knots = ad.kn)4      7.479  6.501   8.605
I(lex.Cst == "Ins")TRUE              2.170  1.948   2.418
I(Per - 2000)                        0.965  0.954   0.977
sexF                                 0.667  0.616   0.723
```

Note that in order for this model to be usable for simulation, it is necessary that we use
the components of the `Lexis` object to specify the survival. Each record in the data frame
`Si` represents follow up from `DMdur` to `DMdur+lex.dur`, so the model is a Cox model with
diabetes duration as underlying timescale and age at diagnosis, `Age-DMdur`, as covariate.

Also note that we used `I(lex.Cst=="Ins")` instead of just `lex.Cst`, because `coxph`
assigns design matrix columns to all levels of `lex.Cst`, also those not present in data,
which would give `NA`s among the parameter estimates and `NA`s as mortality outcomes.

We see that the effect of insulin and the other covariates are pretty much the same as in
the two-time-scale model. We can simulate from this model too; there is no restrictions on
what type of model can be used for different transitions

```
> Tr.c <- list( "DM" = list( "Ins"        = Tr$DM$Ins,
+                            "Dead"       = Cox.Dead  ),
+               "Ins" = list( "Dead(Ins)" = Cox.Dead ) )
> system.time( simC <- simLexis( Tr.c,
+                                ini,
+                              t.range = 12,
+                                  N = Nsim ) )
  bruger    system forløbet
    2.26      0.42     2.69
> summary( simC, by="sex" )
$M

Transitions:
     To
From   DM Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM  171 192  137         0       500      329    3645.74       500
```

```
  Ins   0 123   0        69       192      69   1007.35       192
  Sum 171 315  137        69       692     398   4653.09       500
```

`$F`

```
Transitions:
     To
From   DM Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM  227 185   88         0       500      273   4332.82       500
  Ins   0 138    0        47       185       47    821.79       185
  Sum 227 323   88        47       685      320   5154.61       500
```

1.9   Reporting the simulation results

We can now tabulate the number of persons in each state at a predefined set of times on a given time scale. Note that in order for this to be sensible, the `from` argument would normally be equal to the starting time for the simulated individuals.

```
> system.time(
+ nSt <- nState( subset(simL,sex=="M"),
+              at=seq(0,11,0.2), from=1995, time.scale="Per" ) )
  bruger    system forløbet
    0.07      0.00      0.06
> nSt[1:10,]
       State
when       DM Ins Dead Dead(Ins)
  1995    500   0    0         0
  1995.2 497    2    1         0
  1995.4 486    8    6         0
  1995.6 477   13   10         0
  1995.8 468   16   16         0
  1996   459   20   21         0
  1996.2 448   25   27         0
  1996.4 442   29   28         1
  1996.6 438   31   30         1
  1996.8 429   37   33         1
```

We see that as time goes by, the 500 men slowly move away from the starting state (`DM`).

Based on this table (`nSt` is a table) we can now compute the fractions in each state, or, rather more relevant, the cumulative fraction across the states in some specified order, so that a plot of the stacked probabilities can be made, using either the default rather colorful layout, or a more minimalist version (both in figure 1.3):

```
> pM <- pState( nSt, perm=c(1,2,4,3) )
> head( pM )
       State
when        DM   Ins Dead(Ins) Dead
  1995    1.000 1.000    1.000    1
  1995.2 0.994 0.998    0.998    1
  1995.4 0.972 0.988    0.988    1
  1995.6 0.954 0.980    0.980    1
  1995.8 0.936 0.968    0.968    1
  1996   0.918 0.958    0.958    1
```

```
> par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plot( pM )
> plot( pM, border="black", col="transparent", lwd=3 )
> text( rep(as.numeric(rownames(pM)[nrow(pM)-1]),ncol(pM)),
+       pM[nrow(pM),]-diff(c(0,pM[nrow(pM),]))/5,
+       colnames( pM ), adj=1 )
> box( col="white", lwd=3 )
> box()
```
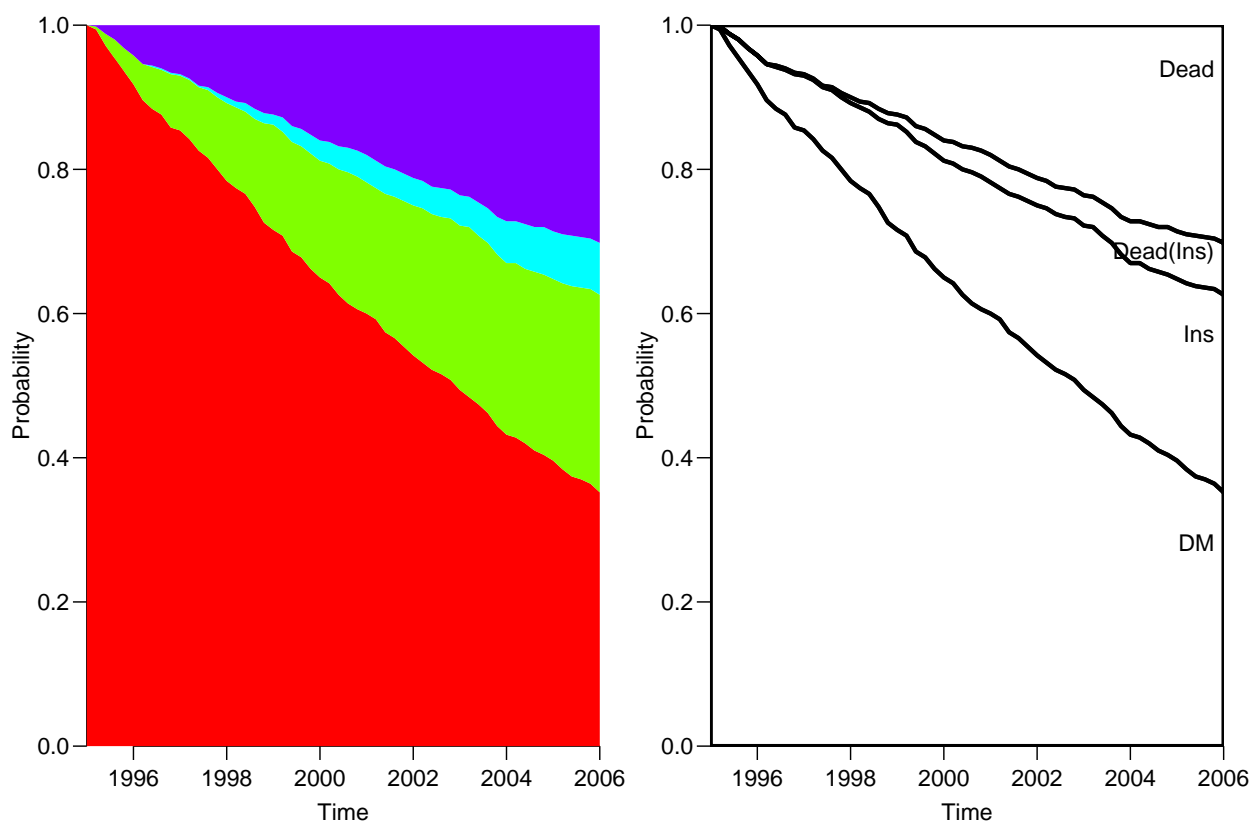

Figure 1.3: *Default layout of the* `plot.pState` *graph (left), and a version with the state probabilities as lines and annotation of states.*   `./simLexis-pstate0`

A more useful set-up of the graph would include a more through annotation and sensible choice of colors, as seen in figure 1.4:

```
> clr <- c("limegreen","orange")
> # expand with a lighter version of the two chosen colors
> clx <- c( clr, rgb( t( col2rgb( clr[2:1] )*2 + rep(255,3) ) / 3, max=255 ) )
> par( mfrow=c(1,2), las=1, mar=c(3,3,4,2), mgp=c(3,1,0)/1.6 )
> # Men
> plot( pM, col=clx, xlab="Date of FU" )
> lines( as.numeric(rownames(pM)), pM[,2], lwd=3 )
> mtext( "60 year old male, diagnosed 1990, aged 55", side=3, line=2.5, adj=0, col=gray(0.6)
> mtext( "Survival curve", side=3, line=1.5, adj=0 )
> mtext( "DM, no insulin   DM, Insulin", side=3, line=0.5, adj=0, col=clr[2] )
> mtext( "DM, no insulin", side=3, line=0.5, adj=0, col=clr[1] )
> axis( side=4 )
> axis( side=4, at=1:19/20, labels=FALSE )
```

```
> axis( side=4, at=1:99/100, labels=FALSE, tcl=-0.3 )
> # Women
> pF <- pState( nState( subset(simL,sex=="F"),
+                       at=seq(0,11,0.2),
+                       from=1995,
+                       time.scale="Per" ),
+             perm=c(1,2,4,3) )
> plot( pF, col=clx, xlab="Date of FU" )
> lines( as.numeric(rownames(pF)), pF[,2], lwd=3 )
> mtext( "60 year old female, diagnosed 1990, aged 55", side=3, line=2.5, adj=0, col=gray(0.
> mtext( "Survival curve", side=3, line=1.5, adj=0 )
> mtext( "DM, no insulin   DM, Insulin", side=3, line=0.5, adj=0, col=clr[2] )
> mtext( "DM, no insulin", side=3, line=0.5, adj=0, col=clr[1] )
> axis( side=4 )
> axis( side=4, at=1:19/20, labels=FALSE )
> axis( side=4, at=1:99/100, labels=FALSE, tcl=-0.3 )
```
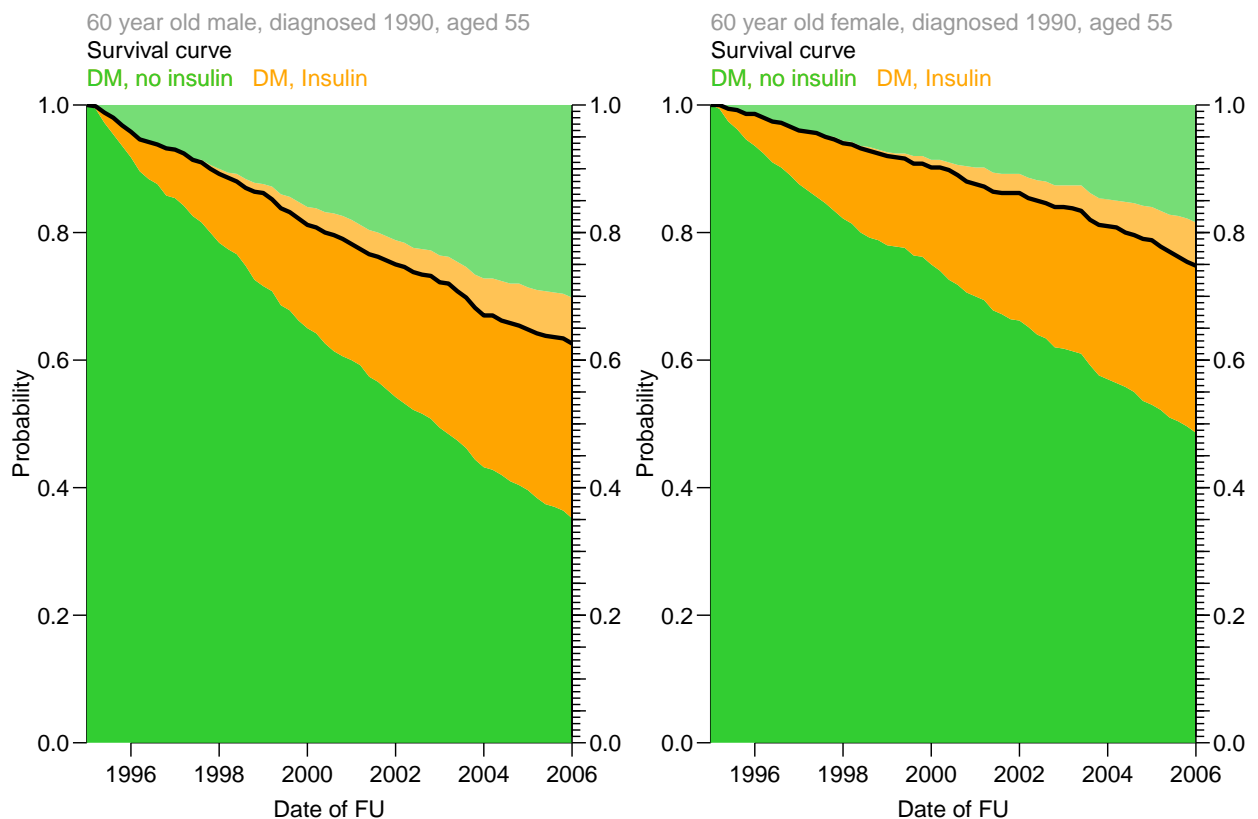

Figure 1.4: `plot.pState` *graphs where persons ever on insulin are given in orange and persons never on insulin in green, and the overall survival (dead over the line) as a black line.*   ./simLexis-pstatex

If we instead wanted to show the results on the age-scale, we would use age as timescale when constructing the probabilities; otherwise the code is pretty much the same as before (Figure 1.5):

```
> par( mfrow=c(1,2), las=1, mar=c(3,3,4,2), mgp=c(3,1,0)/1.6 )
> # Men
> pM <- pState( nState( subset(simL,sex=="M"),
```

```
+                        at=seq(0,11,0.2),
+                        from=60,
+                        time.scale="Age" ),
+                perm=c(1,2,4,3) )
> plot( pM, col=clx, xlab="Age" )
> lines( as.numeric(rownames(pM)), pM[,2], lwd=3 )
> mtext( "60 year old male, diagnosed 1990, aged 55", side=3, line=2.5, adj=0, col=gray(0.6)
> mtext( "Survival curve", side=3, line=1.5, adj=0 )
> mtext( "DM, no insulin   DM, Insulin", side=3, line=0.5, adj=0, col=clr[2] )
> mtext( "DM, no insulin", side=3, line=0.5, adj=0, col=clr[1] )
> axis( side=4 )
> axis( side=4, at=1:19/20, labels=FALSE )
> axis( side=4, at=1:19/20, labels=FALSE, tcl=-0.4 )
> axis( side=4, at=1:99/100, labels=FALSE, tcl=-0.3 )
> # Women
> pF <- pState( nState( subset(simL,sex=="F"),
+                        at=seq(0,11,0.2),
+                        from=60,
+                        time.scale="Age" ),
+                perm=c(1,2,4,3) )
> plot( pF, col=clx, xlab="Age" )
> lines( as.numeric(rownames(pF)), pF[,2], lwd=3 )
> mtext( "60 year old female, diagnosed 1990, aged 55", side=3, line=2.5, adj=0, col=gray(0.(
> mtext( "Survival curve", side=3, line=1.5, adj=0 )
> mtext( "DM, no insulin   DM, Insulin", side=3, line=0.5, adj=0, col=clr[2] )
> mtext( "DM, no insulin", side=3, line=0.5, adj=0, col=clr[1] )
> axis( side=4 )
> axis( side=4, at=1:9/10, labels=FALSE )
> axis( side=4, at=1:19/20, labels=FALSE, tcl=-0.4 )
> axis( side=4, at=1:99/100, labels=FALSE, tcl=-0.3 )
```

Note the several statements with `axis(side=4,...`; they are necessary to get the fine tick-marks in the right hand side of the plots that you will need in order to read off the probabilities at 2006 (or 71 years).

1.9.1   Comparing predictions from different models

We have actually fitted different models for the transitions, and we have simulated Lexis objects from all three approaches, so we can plot these predictions on top of each other:

```
> PrM  <- pState( nState( subset(simP,sex=="M"),
+                        at=seq(0,11,0.2),
+                        from=60,
+                        time.scale="Age" ),
+                perm=c(1,2,4,3) )
> PrF  <- pState( nState( subset(simP,sex=="F"),
+                        at=seq(0,11,0.2),
+                        from=60,
+                        time.scale="Age" ),
+                perm=c(1,2,4,3) )
> CoxM <- pState( nState( subset(simC,sex=="M"),
+                        at=seq(0,11,0.2),
+                        from=60,
+                        time.scale="Age" ),
+                perm=c(1,2,4,3) )
> CoxF <- pState( nState( subset(simC,sex=="F"),
```
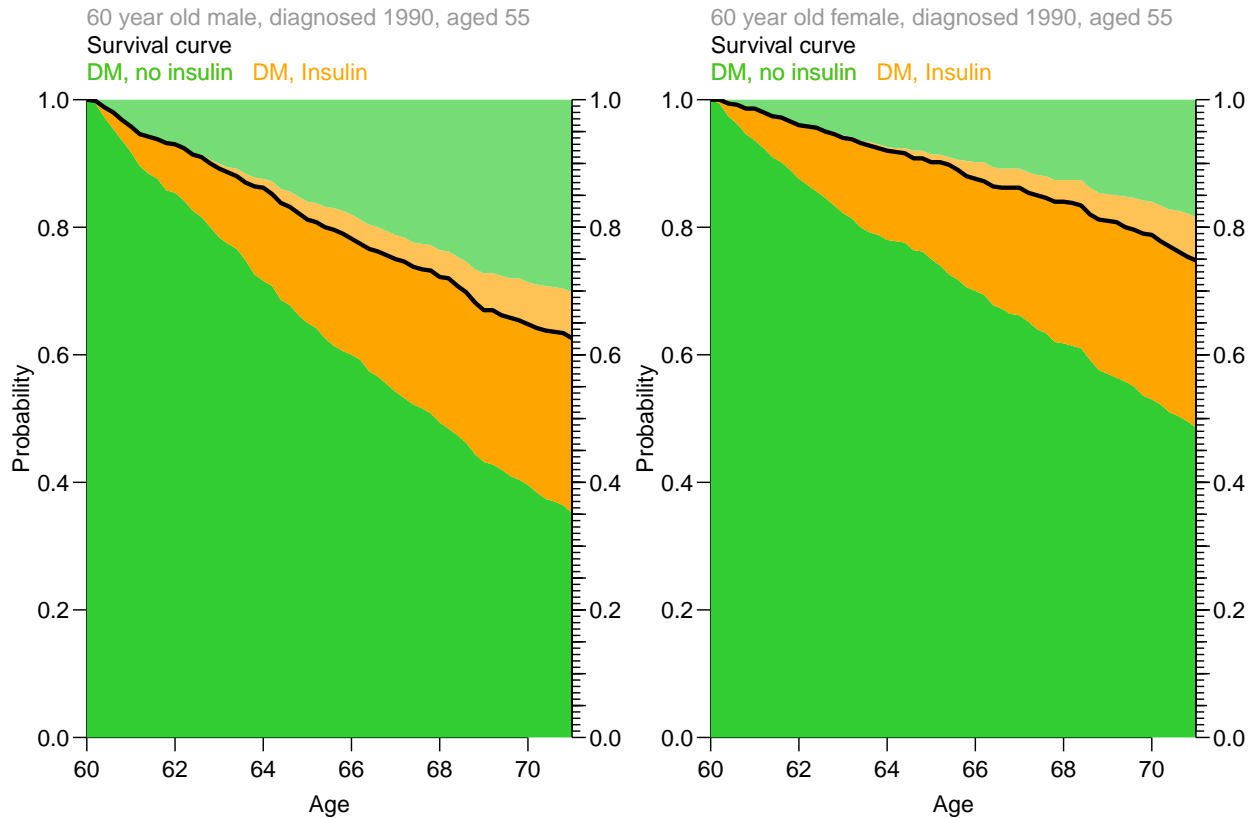
Figure 1.5: `plot.pState` *graphs where persons ever on insulin are given in orange and persons never on insulin in green, and the overall survival (dead over the line) as a black line.*   `./simLexis-pstatey`

```
+                          at=seq(0,11,0.2),
+                          from=60,
+                          time.scale="Age" ),
+                   perm=c(1,2,4,3) )
> par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
>  plot(   pM, border="black", col="transparent", lwd=3 )
> lines(  PrM, border="blue" , col="transparent", lwd=3 )
> lines( CoxM, border="red"  , col="transparent", lwd=3 )
> text( 60.5, 0.05, "M" )
> box( lwd=5, col="white" ) ; box( lwd=2, col="black" )
>  plot(   pF, border="black", col="transparent", lwd=3 )
> lines(  PrF, border="blue" , col="transparent", lwd=3 )
> lines( CoxF, border="red"  , col="transparent", lwd=3 )
> text( 60.5, 0.05, "F" )
> box( lwd=5, col="white" ) ; box( lwd=2, col="black" )
```

From figure 1.6 it is clear that the two proportional hazards models (blue and red curves) produce pretty much the same estimates of the state occupancy probabilities over time, but also that they relative to the model with separately estimated transition intensities overestimates the probability of being alive without insulin and underestimates the probabilities of being dead without insulin. However both the overall survival, and the fraction of persons on insulin are quite well in agreement with the more elaborate model. Thus the proportional hazards models overestimate the relative mortality of the insulin
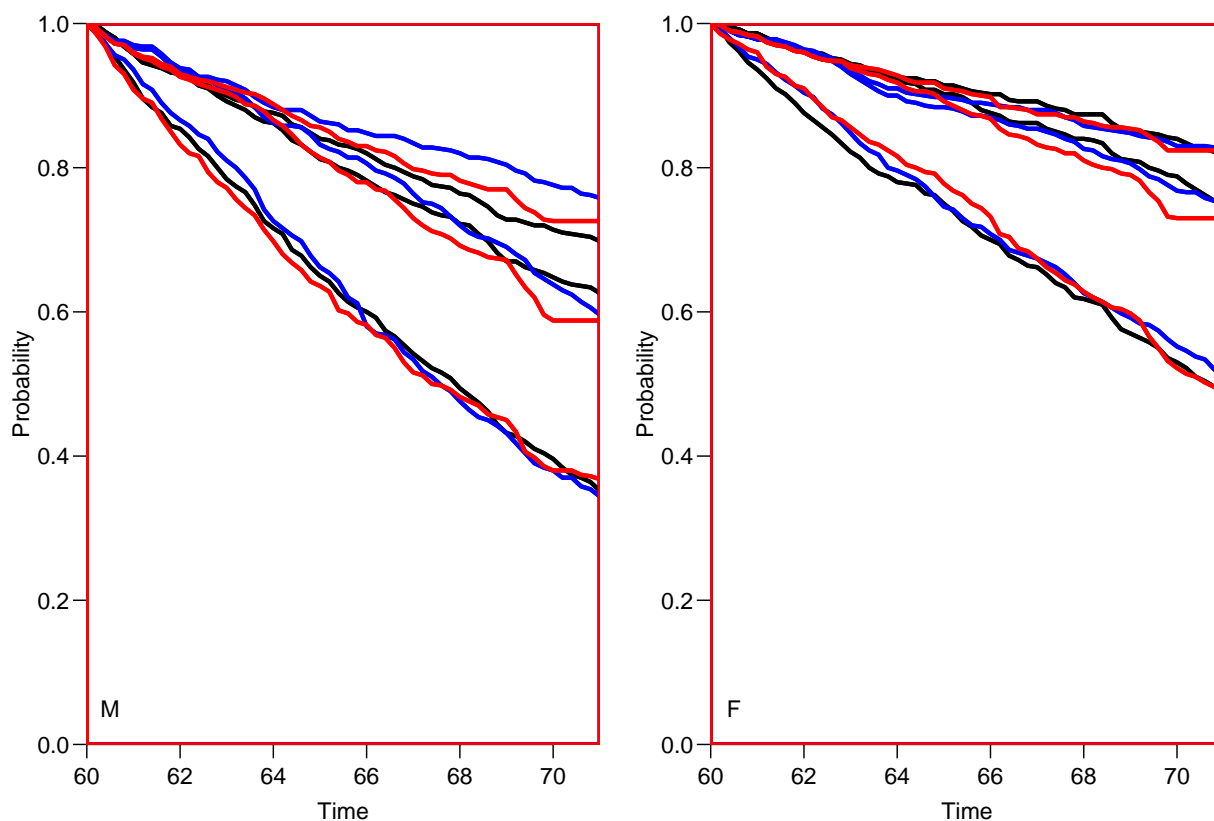
Figure 1.6: *Comparison of the simulated state occupancy probabilities using separate Poisson models for the mortality rates with and without insulin (black) and using proportional hazards Poisson models (blue) and Cox-models with diabetes duration as timescale and age at diabetes diagnosis as covariate (red).* ./simLexis-comp-0

treated diabetes patients relative to the non-insulin treated.

Interestingly, we also see a bump in the estimated probabilities from the Cox-model based model, but this is entirely an artifact that comes from the estimation method for the baseline hazard of the Cox-model that lets the (cumulative) hazard have large jumps at event times where the risk set is small. So also here it shows up that an assumption of continuous underlying hazards leads to more credible estimates.

Chapter 2

Simulation of transitions in multistate models

2.1 Theory

Suppose that the rate functions for the transitions out of the current state to, say, 3 different states are λ_1, λ_2 and λ_3, and the corresponding cumulative rates are Λ_1, Λ_2 and Λ_3, and we want to simulate an exit time and an exit state (that is either 1, 2 or 3). This can be done in two slightly different ways:

1. First time, then state:

   (a) Compute the survival function, $S(t) = \exp\big(-\Lambda_1(t) - \Lambda_2(t) - \Lambda_3(t)\big)$

   (b) Simulate a random U(0,1) variate, u, say.

   (c) The simulated exit time is then the solution t_u to the equation
   $S(t_u) = u \quad \Leftrightarrow \quad \sum_j \Lambda_j(t_u) = -\log(u)$.

   (d) A simulated transition at t_u is then found by simulating a random draw from the multinomial distribution with probabilities $p_i = \lambda_i(t_u)/\sum_j \lambda_j(t_u)$.

2. Separate cumulative incidences:

   (a) Simulate 3 independent U(0,1) random variates u_1, u_2 and u_3.

   (b) Solve the equations $\Lambda_i(t_i) = -\log(u_i), i = 1, 2, 3$ and get (t_1, t_2, t_3).

   (c) The simulated survival time is then $\min(t_1, t_2, t_3)$, and the simulated transition is to the state corresponding to this, that is $k \in \{1, 2, 3\}$, where $t_k = \min(t_1, t_2, t_3)$

The intuitive argument is that with three possible transition there are 3 independent processes running, but only the first transition is observed. The latter approach is used in the implementation in `simLexis`.

The formal argument for the equality of the two approaches goes as follows:

1. Equality of the transition times:

(a) In the first approach we simulate from a distribution with cumulative rate $\Lambda_1(t) + \Lambda_2(t) + \Lambda_3(t)$, hence from a distribution with survival function:

$$S(t) = \exp\big(-(\Lambda_1(t) + \Lambda_2(t) + \Lambda_3(t))\big)$$
$$= \exp\big(-\Lambda_1(t)\big) \times \exp\big(-\Lambda_2(t)\big) \times \exp\big(-\Lambda_3(t)\big)$$

(b) In the second approach we choose the smallest of three independent survival times, with survival functions $\exp(-\Lambda_i), i = 1, 2, 3$. Now, the survival function for the minimum of three independent survival times is:

$$S_{\min}(t) = \mathrm{P}\{\min(t_1, t_2, t_3) > t\}$$
$$= \mathrm{P}\{t_1 > t\} \times \mathrm{P}\{t_2 > t\} \times \mathrm{P}\{t_3 > t\}$$
$$= \exp\big(-\Lambda_1(t)\big) \times \exp\big(-\Lambda_2(t)\big) \times \exp\big(-\Lambda_3(t)\big)$$

which is the same survival function as derived above.

2. Type of transition:

(a) In the first instance the probability of a transition to state i, conditional on the transition time being t, is as known from standard probability theory: $\lambda_i(t)/\big(\lambda_1(t) + \lambda_2(t) + \lambda_3(t)\big)$.

(b) In the second approach we choose the transition corresponding to the the smallest of the transition times. So when we condition on the event that a transition takes place at time t, we have to show that the conditional probability that the smallest of the three simulated transition times was actually the ith, is as above.

But conditional on *survival* till t, the probabilities that events of type $1, 2, 3$ takes place in the interval $(t, t + \mathrm{d}t)$ are $\lambda_1(t)\,\mathrm{d}t$, $\lambda_2(t)\,\mathrm{d}t$ and $\lambda_1(t)\,\mathrm{d}t$, respectively (assuming that the probability of more than one event in the interval of length $\mathrm{d}t$ is 0). Hence the conditional probabilities *given a transition time* in $(t, t + \mathrm{d}t)$ is:

$$\frac{\lambda_i(t)\,\mathrm{d}t}{\lambda_1(t)\,\mathrm{d}t + \lambda_2(t)\,\mathrm{d}t + \lambda_3(t)\,\mathrm{d}t} = \frac{\lambda_i(t)}{\lambda_1(t) + \lambda_2(t) + \lambda_3(t)}$$

— exactly as above.

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  Start time: 2025-01-13, 09:23:28
    End time: 2025-01-13, 09:23:48
Elapsed time: 0.33 minutes
```

Bibliography

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