

Multistate models in Epi: The DLI example from JSS: the etm package by Allignol *et al.*

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1 Introduction

This is an illustration of how to set up the multistate data from `dli.data` used as illustration in [1]. In this note I use the `Lexis` machinery from the `Epi` package [3, 2], which makes things more transparent, because it requires an initial specification of the multistate *data* in terms of transitions and timescales. The latter is largely bypassed as an issue in [1] as only one time scale is used. The `Lexis` machinery also includes a couple of summary and graphical functions that facilitate the overview of the data.

We have downloaded the data, and we start by loading the `Epi` package and the data:

```
> options( width=90 )
> library( Epi )
> library( etm )
> library( survival )
> library( splines )
> print( sessionInfo(), l=F )
R version 3.0.2 (2013-09-25)
Platform: i386-w64-mingw32/i386 (32-bit)

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

other attached packages:
[1] etm_0.6      survival_2.37-4 Epi_1.1.61    foreign_0.8-55

loaded via a namespace (and not attached):
[1] grid_3.0.2    lattice_0.20-23 parallel_3.0.2 tools_3.0.2

> # clear()
> # lls()
> # load( url("http://www.jstatsoft.org/v38/i04/supp/3") )
> # save( dli.data, file="./data/dli.Rda" )
> load( file="./data/dli.Rda" )
> str( dli.data )

'data.frame':
  536 obs. of  5 variables:
 $ id      : int  2 3 4 5 6 11 12 13 15 16 ...
 $ from    : num  0 0 0 0 0 0 0 0 0 0 ...
 $ to      : chr  "cens" "cens" "cens" "cens" ...
 $ time    : num  19.9 15.2 21 16 21.1 ...
 $ distatpr: int  1 1 1 2 1 1 1 1 1 1 ...
```

In order to understand how data is coded we list data for a few select persons:

```
> subset( dli.data, id %in% c(2,5,388,511,531,600) )

  id from to time distatpr
1  2  0 cens 19.8841843    1
4  5  0 cens 16.0316320    2
202 388 0  2  2.8467381    1
203 388 2 cens 3.8754478    1
328 511 0  2  0.3127550    1
329 511 2  4  0.6354438    1
330 511 4 cens 1.3810754    1
355 531 0  2  0.4244171    3
356 531 2  4  0.4117015    3
357 531 4  5  0.5622658    3
505 600 0  2  0.4632695    1
506 600 2  4  1.0560224    1
507 600 4  6  1.3696801    1
508 600 6 cens 3.0239852    1
```

The time records from persons 531 is clearly flawed because exit from state 2 occurs before entry to it. There is only this one instance in the dataset:

```
> subset( dli.data, c(TRUE,diff(time)<0 & diff(id)==0 ) )
      id from to      time distatpr
1     2    0 cens 19.8841843      1
356 531    2    4  0.4117015      3
```

So we doctor it (more or less arbitrarily):

```
> dli.data[dli.data$id==531 & dli.data$from==2,"time"] <- 0.45
```

We can now inspect how the transitions occur between states:

```
> with( dli.data, table( from, to ) )
      to
from  1  2  3  4  5  6  7  8 cens
0  100 123  0  0  0  0  0  0  81
2   0  0  40 65  0  0  0  0  18
4   0  0  0  0  10 44  0  0  11
6   0  0  0  0  0  0  2  4  38
```

1.1 Setting up a Lexis object

In order to be able to put the data into a Lexis object, we must know the entry times for each state, not only the exit times. This is done by using the `ave` function, that allows operation within each level of a grouping (in this case `id`). Moreover, we also change the censoring value "cens" to the value of the state in which the censoring occurs (`as.numeric("cens")` returns NA).

```
> dli <- transform( dli.data,
+                  to = as.numeric(to),
+                  ti = ave( time, id, FUN=function( x ) c(0,x[-length(x)]) ) )
> dli$to <- ifelse( is.na(dli$to), dli$from, dli$to )
> subset( dli, id %in% c(5,388,511,600) )
```

```
      id from to      time distatpr      ti
4     5    0  0 16.0316320      2 0.0000000
202 388    0  2  2.8467381      1 0.0000000
203 388    2  2  3.8754478      1 2.8467381
328 511    0  2  0.3127550      1 0.0000000
329 511    2  4  0.6354438      1 0.3127550
330 511    4  4  1.3810754      1 0.6354438
505 600    0  2  0.4632695      1 0.0000000
506 600    2  4  1.0560224      1 0.4632695
507 600    4  6  1.3696801      1 1.0560224
508 600    6  6  3.0239852      1 1.3696801
```

```
> with( dli, table( from, to ) )
```

```
      to
from  0  1  2  3  4  5  6  7  8
0  81 100 123  0  0  0  0  0  0
2   0  0  18 40 65  0  0  0  0
4   0  0  0  0  11 10 44  0  0
6   0  0  0  0  0  0  38  2  4
```

1.1.1 Other timescales

Apart from the underlying timescale, time from inclusion in the study (*i.e.* treatment to remission), it may be of interest to be able to assess the effect of other timescales, such as

current age and calendar time. These are not available in the data set and might even not be relevant depending on the range of these in data.

However it would be most interesting to be able to use the time since entry into each of the three intermediate states. So for the state 2 (1st relapse) we can construct the time of entry into the state and subsequently the time *since* entry for all other pieces of follow-up:

```
> tmp <- subset(dli,to==2 & from!=to)[,c("id","time")]
> names(tmp)[2] <- "tr"
> dli <- merge( dli, tmp, all.x=TRUE )
> dli$tr <- with( dli, ifelse( ti-tr>=0, ti-tr, NA ) )
> subset(dli,id %in% c(600,603,608) )
```

	id	from	to	time	distatpr	ti	tr
505	600	0	2	0.4632695	1	0.0000000	NA
506	600	2	4	1.0560224	1	0.4632695	0.0000000
507	600	4	6	1.3696801	1	1.0560224	0.5927529
508	600	6	6	3.0239852	1	1.3696801	0.9064107
513	603	0	2	1.9036507	1	0.0000000	NA
514	603	2	4	2.7898033	1	1.9036507	0.0000000
515	603	4	6	3.9490625	1	2.7898033	0.8861527
516	603	6	7	8.8798961	1	3.9490625	2.0454118
525	608	0	2	3.8078026	1	0.0000000	NA
526	608	2	4	4.7707204	1	3.8078026	0.0000000
527	608	4	6	5.4684705	1	4.7707204	0.9629178
528	608	6	8	5.7731360	1	5.4684705	1.6606679

```
> str( dli )
'data.frame':      536 obs. of  7 variables:
 $ id      : int  2 3 4 5 6 11 12 13 15 16 ...
 $ from    : num  0 0 0 0 0 0 0 0 0 0 ...
 $ to      : num  0 0 0 0 0 0 0 0 0 0 ...
 $ time    : num  19.9 15.2 21 16 21.1 ...
 $ distatpr: int  1 1 1 2 1 1 1 1 1 1 ...
 $ ti      : num  0 0 0 0 0 0 0 0 0 0 ...
 $ tr      : num  NA NA NA NA NA NA NA NA NA NA ...
```

The same is now repeated for the other two intermediate states:

```
> # DLI
> tmp <- subset(dli,to==4 & from!=to)[,c("id","time")]
> names(tmp)[2] <- "tD"
> dli <- merge( dli, tmp, all.x=TRUE )
> dli$tD <- with( dli, ifelse( ti-tD>=0, ti-tD, NA ) )
> # Rm2
> tmp <- subset(dli,to==6 & from!=to)[,c("id","time")]
> names(tmp)[2] <- "tR"
> dli <- merge( dli, tmp, all.x=TRUE )
> dli$tR <- with( dli, ifelse( ti-tR>=0, ti-tR, NA ) )
> subset(dli,id %in% c(600,603,608) )
```

	id	from	to	time	distatpr	ti	tr	tD	tR
505	600	0	2	0.4632695	1	0.0000000	NA	NA	NA
506	600	2	4	1.0560224	1	0.4632695	0.0000000	NA	NA
507	600	4	6	1.3696801	1	1.0560224	0.5927529	0.0000000	NA
508	600	6	6	3.0239852	1	1.3696801	0.9064107	0.3136578	0
513	603	0	2	1.9036507	1	0.0000000	NA	NA	NA
514	603	2	4	2.7898033	1	1.9036507	0.0000000	NA	NA
515	603	4	6	3.9490625	1	2.7898033	0.8861527	0.0000000	NA
516	603	6	7	8.8798961	1	3.9490625	2.0454118	1.1592591	0
525	608	0	2	3.8078026	1	0.0000000	NA	NA	NA
526	608	2	4	4.7707204	1	3.8078026	0.0000000	NA	NA
527	608	4	6	5.4684705	1	4.7707204	0.9629178	0.0000000	NA
528	608	6	8	5.7731360	1	5.4684705	1.6606679	0.6977501	0

Now we can define a Lexis object, using the factor facility in R to label the states:

```

> state.names <- c("Rem" , "D/Rem",
+                 "Rel" , "D/Rel",
+                 "DLI" , "D/DLI",
+                 "Rem2" , "D/Rem2",
+                 "Rel2")
> dli <- Lexis( entry      = list( tfi=ti, tfr=tr, tfD=tD, tFR=tR ),
+              entry.status = factor( from, levels=0:8, labels=state.names ),
+              exit       = list( tfi=time ),
+              exit.status = factor( to, levels=0:8, labels=state.names ),
+              id = id,
+              data = dli )
> print.data.frame(
+ subset( dli, id %in% c(600,603,608) )[,1:13], digits=3)

```

	tfi	tfr	tfD	tFR	lex.dur	lex.Cst	lex.Xst	lex.id	id	from	to	time	distatpr
505	0.000	NA	NA	NA	0.463	Rem	Rel	600	600	0	2	0.463	1
506	0.463	0.000	NA	NA	0.593	Rel	DLI	600	600	2	4	1.056	1
507	1.056	0.593	0.000	NA	0.314	DLI	Rem2	600	600	4	6	1.370	1
508	1.370	0.906	0.314	0	1.654	Rem2	Rem2	600	600	6	6	3.024	1
513	0.000	NA	NA	NA	1.904	Rem	Rel	603	603	0	2	1.904	1
514	1.904	0.000	NA	NA	0.886	Rel	DLI	603	603	2	4	2.790	1
515	2.790	0.886	0.000	NA	1.159	DLI	Rem2	603	603	4	6	3.949	1
516	3.949	2.045	1.159	0	4.931	Rem2	D/Rem2	603	603	6	7	8.880	1
525	0.000	NA	NA	NA	3.808	Rem	Rel	608	608	0	2	3.808	1
526	3.808	0.000	NA	NA	0.963	Rel	DLI	608	608	2	4	4.771	1
527	4.771	0.963	0.000	NA	0.698	DLI	Rem2	608	608	4	6	5.468	1
528	5.468	1.661	0.698	0	0.305	Rem2	Rel2	608	608	6	8	5.773	1

Setting up a Lexis object for this dataset basically means replacing the time of event for each transition by the time of entry into a state (`tfi`) and the sojourn time (`lex.dur`) in the state, and making clear that with this convention `from` (or `lex.Cst`) is the state in which the person spends `lex.dur`, and `to` (or `lex.Xst`) is the state to which the persons moves (using the convention that if `from=to` we have a censored observation).

Using the summary facility for Lexis objects shows the transitions and the risk time in each state:

```

> summary( dli )

```

Transitions:													
To													
From	Rem	D/Rem	Rel	D/Rel	DLI	D/DLI	Rem2	D/Rem2	Rel2	Records:	Events:	Risk time:	
Rem	81	100	123	0	0	0	0	0	0	304	223	1042.59	
Rel	0	0	18	40	65	0	0	0	0	123	105	246.98	
DLI	0	0	0	0	11	10	44	0	0	65	54	92.18	
Rem2	0	0	0	0	0	0	38	2	4	44	6	189.38	
Sum	81	100	141	40	76	10	82	2	4	536	388	1571.13	

```


```

Transitions:	
To	
From	Persons:
Rem	304
Rel	123
DLI	65
Rem2	44
Sum	304

There is also a facility to show the states in a graph with person-years (risk time in the units given) shown in the boxes and no. of transitions shown between them:

```

> boxes( dli )

```

This is an interactive facility where you are asked to click on the plot where the boxes should go; but you can also explicitly supply the positions of the centers of the boxes. For

later use we first define the number of states, and a set of colors to be used for the states in this and subsequent plots. We also scale the printed transition rates between states by 100, so they will appear as percent per year.

```
> n.st <- nlevels( dli$lex.Cst )
> st.col <- rainbow( n.st )
> # A slightly more transparent color
> substr(st.col,8,9) <- "BB"
> boxes( dli, wmult=1.1,
+         boxpos=list(x=c(10,30,30,50,50,70,70,90,90),
+                       y=c(25, 8,42,25,59,42,76,59,93)),
+         col.bg=st.col, scale.R=100, show.BE=TRUE )
```

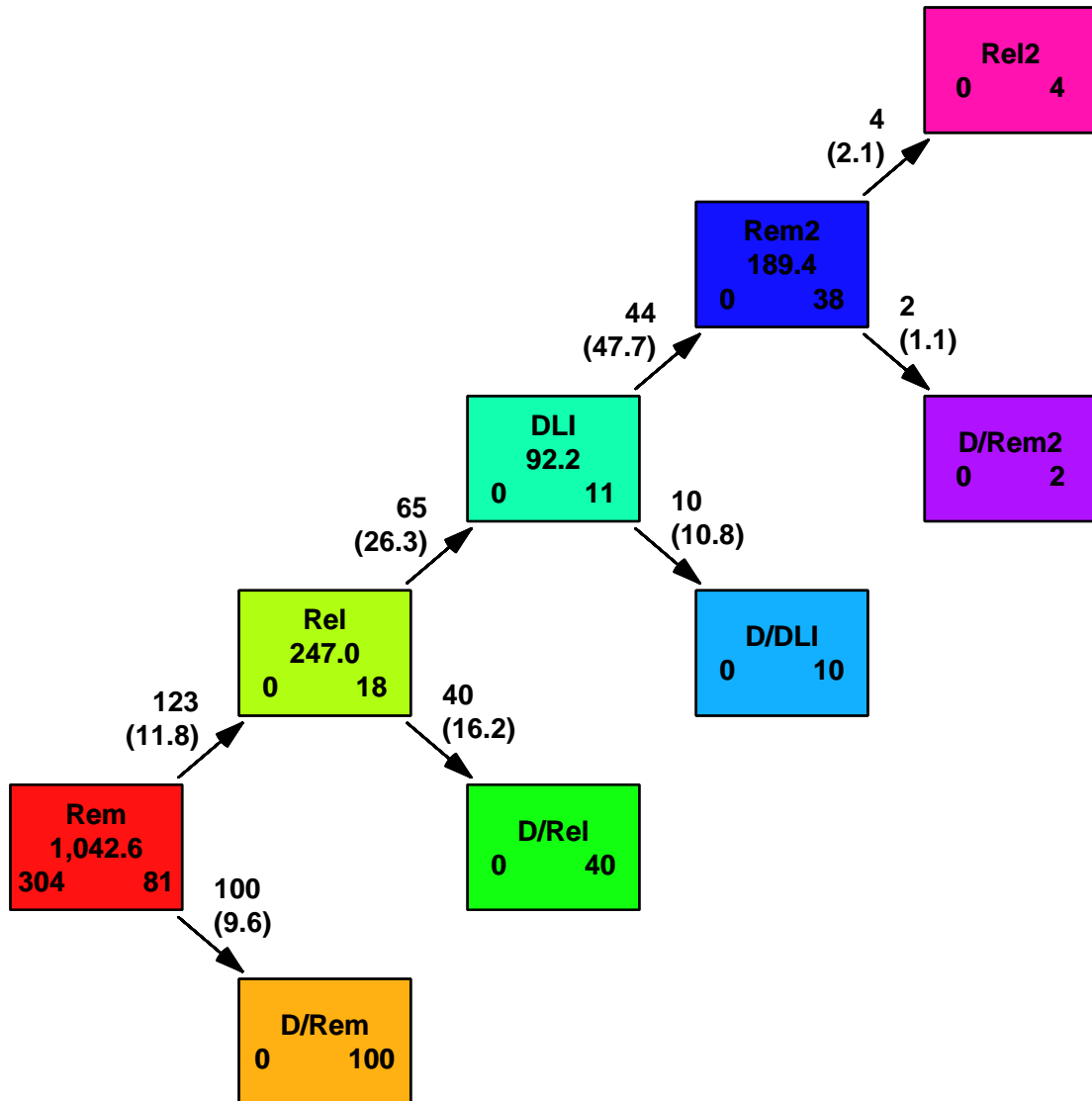


Figure 1: *Display of the actually occurring transitions and -rates (in %/yera) and the corresponding risk time in each state. In each state is also shown the number of persons that start and end in each state. Note that the two rightmost boxes are interchanged relative to the figure 4 in [1] in order to have all mortality rates point down to the right.*

2 The mortality rates

Once the data is set up in a `Lexis` object is quite easy to model the mortality rates. If a joint model for all transition rates is to be set up, we need a stacked dataset; that is a dataset with person years and events for each of the transitions. This means (for this model) that in the stacked dataset all person-years are represented twice, one time for each transition (and all transient states have two transitions out of them):

```
> st.dli <- stack( dli )
> str( st.dli )
Classes 'stacked.Lexis' and 'data.frame':      1072 obs. of  19 variables:
 $ tfi      : num  0 0 0 0 0 0 0 0 0 0 ...
 $ tfr      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tfD      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tFR      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ lex.dur  : num  19.9 15.2 21 16 21.1 ...
 $ lex.Cst  : Factor w/ 9 levels "Rem","D/Rem",...: 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Xst  : Factor w/ 9 levels "Rem","D/Rem",...: 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Tr   : Factor w/ 8 levels "Rem->D/Rem","Rem->Rel",...: 1 1 1 1 1 1 1 1 ...
 $ lex.Fail: logi  FALSE FALSE FALSE FALSE FALSE FALSE ...
 $ lex.id   : int   2 3 4 5 6 11 12 13 15 16 ...
 $ id       : int   2 3 4 5 6 11 12 13 15 16 ...
 $ from     : num   0 0 0 0 0 0 0 0 0 0 ...
 $ to       : num   0 0 0 0 0 0 0 0 0 0 ...
 $ time     : num  19.9 15.2 21 16 21.1 ...
 $ distatpr: int   1 1 1 2 1 1 1 1 1 1 ...
 $ ti       : num   0 0 0 0 0 0 0 0 0 0 ...
 $ tr       : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tD       : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tR       : num  NA NA NA NA NA NA NA NA NA NA ...
 - attr(*, "breaks")=List of 4
 ..$ tfi: NULL
 ..$ tfr: NULL
 ..$ tfD: NULL
 ..$ tFR: NULL
 - attr(*, "time.scales")= chr  "tfi" "tfr" "tfD" "tFR"

> round(
+ cbind( "Original"=with( dli, tapply( lex.dur, lex.Cst, sum ) ),
+       "Stacked" =with( st.dli, tapply( lex.dur, lex.Cst, sum ) ) ), 1 )
      Original Stacked
Rem      1042.6  2085.2
D/Rem      NA      NA
Rel      247.0   494.0
D/Rel      NA      NA
DLI       92.2   184.4
D/DLI      NA      NA
Rem2     189.4   378.8
D/Rem2     NA      NA
Rel2      NA      NA

> round( xtabs( cbind( lex.Fail, lex.dur ) ~ lex.Tr, data = st.dli ), 1 )
lex.Tr      lex.Fail lex.dur
Rem->D/Rem    100.0  1042.6
Rem->Rel      123.0  1042.6
Rel->D/Rel     40.0   247.0
Rel->DLI       65.0   247.0
DLI->D/DLI    10.0    92.2
DLI->Rem2     44.0    92.2
Rem2->D/Rem2   2.0   189.4
Rem2->Rel2     4.0   189.4
```

For the analysis of the deaths we need only the transitions 1,3,5 and 7:

```
> dd.dli <- subset( st.dli, lex.Tr %in% levels(lex.Tr)[c(1,3,5,7)] )
> table( dd.dli$lex.Tr )
      Rem->D/Rem  Rem->Rel  Rel->D/Rel  Rel->DLI  DLI->D/DLI  DLI->Rem2
      304         0        123         0         65         0
Rem2->D/Rem2  Rem2->Rel2
      44         0
```

In order not to mess up the reporting etc. we remove the non-existent levels of the factor `lex.Tr`:

```
> dd.dli$lex.Tr <- factor( dd.dli$lex.Tr )
> round( xtabs( cbind( lex.Fail, lex.dur ) ~ lex.Tr, data=dd.dli ), 1 )
lex.Tr      lex.Fail  lex.dur
Rem->D/Rem    100.0  1042.6
Rel->D/Rel    40.0   247.0
DLI->D/DLI    10.0   92.2
Rem2->D/Rem2   2.0   189.4
```

Now we can do a Cox-analysis using time as the underlying timescale, and assuming that the mortality rates are proportional on this scale:

```
> str( dd.dli )
Classes 'stacked.Lexis' and 'data.frame':      536 obs. of  19 variables:
 $ tfi      : num  0 0 0 0 0 0 0 0 0 0 ...
 $ tfr      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tfD      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tfr      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ lex.dur  : num  19.9 15.2 21 16 21.1 ...
 $ lex.Cst  : Factor w/ 9 levels "Rem","D/Rem",...: 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Xst  : Factor w/ 9 levels "Rem","D/Rem",...: 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Tr   : Factor w/ 4 levels "Rem->D/Rem","Rel->D/Rel",...: 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Fail: logi  FALSE FALSE FALSE FALSE FALSE FALSE ...
 $ lex.id   : int   2 3 4 5 6 11 12 13 15 16 ...
 $ id       : int   2 3 4 5 6 11 12 13 15 16 ...
 $ from     : num   0 0 0 0 0 0 0 0 0 0 ...
 $ to       : num   0 0 0 0 0 0 0 0 0 0 ...
 $ time     : num   19.9 15.2 21 16 21.1 ...
 $ distatpr: int   1 1 1 2 1 1 1 1 1 1 ...
 $ ti       : num   0 0 0 0 0 0 0 0 0 0 ...
 $ tr       : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tD       : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tR       : num  NA NA NA NA NA NA NA NA NA NA ...
 - attr(*, "breaks")=List of 4
 ..$ tfi: NULL
 ..$ tfr: NULL
 ..$ tfD: NULL
 ..$ tfr: NULL
 - attr(*, "time.scales")= chr  "tfi" "tfr" "tfD" "tfr"

> c0 <- coxph( Surv(tfi,tfi+lex.dur,lex.Fail) ~ lex.Tr, data=dd.dli )
> summary( c0 )

Call:
coxph(formula = Surv(tfi, tfi + lex.dur, lex.Fail) ~ lex.Tr,
      data = dd.dli)

n= 536, number of events= 152

              coef exp(coef) se(coef)      z Pr(>|z|)
lex.TrRel->D/Rel  1.2396    3.4544  0.2103  5.895 3.75e-09
lex.TrDLI->D/DLI  1.1652    3.2064  0.3604  3.233 0.00123
lex.TrRem2->D/Rem2 -0.9073    0.4036  0.7320 -1.239 0.21518

              exp(coef) exp(-coef) lower .95 upper .95
lex.TrRel->D/Rel    3.4544    0.2895  2.28756    5.216
```

```
lex.TrDLI->D/DLI      3.2064      0.3119      1.58203      6.499
lex.TrRem2->D/Rem2    0.4036      2.4775      0.09614      1.695
```

```
Concordance= 0.573 (se = 0.013 )
Rsquare= 0.073 (max possible= 0.95 )
Likelihood ratio test= 40.41 on 3 df, p=8.721e-09
Wald test = 42.01 on 3 df, p=3.998e-09
Score (logrank) test = 47.96 on 3 df, p=2.171e-10
```

We see that this is pretty consistent with patients being in remission having a lower mortality than those in relapse, and with no real difference between types of relapse (“Rel” or “DLI”). A formal pooling of levels can be achieved by:

```
> dd.dli$Rst <- Relevel( dd.dli$lex.Tr, list(Remis=c(1,4),Relapse=2:3) )
> with( dd.dli, table( lex.Tr, Rst ) )

      Rst
lex.Tr Remis Relapse
Rem->D/Rem      304      0
Rel->D/Rel       0     123
DLI->D/DLI       0     65
Rem2->D/Rem2     44      0

> c1 <- coxph( Surv(tfi,tfi+lex.dur,lex.Fail) ~ Rst, data=dd.dli )
> summary( c1 )

Call:
coxph(formula = Surv(tfi, tfi + lex.dur, lex.Fail) ~ Rst, data = dd.dli)

      n= 536, number of events= 152

              coef exp(coef) se(coef)      z Pr(>|z|)
RstRelapse 1.2829      3.6072  0.1982  6.473  9.6e-11

              exp(coef) exp(-coef) lower .95 upper .95
RstRelapse      3.607      0.2772      2.446      5.319

Concordance= 0.57 (se = 0.012 )
Rsquare= 0.069 (max possible= 0.95 )
Likelihood ratio test= 38.38 on 1 df, p=5.837e-10
Wald test = 41.9 on 1 df, p=9.604e-11
Score (logrank) test = 46.75 on 1 df, p=8.051e-12

> anova( c0, c1, test="Chisq" )

Analysis of Deviance Table
Cox model: response is Surv(tfi, tfi + lex.dur, lex.Fail)
Model 1: ~ lex.Tr
Model 2: ~ Rst
      loglik  Chisq Df P(>|Chi|)
1 -781.39
2 -782.41 2.0352 2 0.3615
```

We now leave the Cox-model and turn to a more natural model for the underlying rates; a model that assumes a hazard smoothly varying by time since initiation.

2.1 Parametric description of rates

If we want to get an overview of how mortality rates actually look as a function of time since entry into the study, we can invoke a Poisson model for time-split data. From the summary on page 4 we see that the total amount of follow-up is about 1500 PY among some 300 patients, so roughly 5 years per person. Hence we split data in pieces of 1/10 year:

```
> sp.dli <- splitLexis( dli, breaks=seq(0,50,1/10) )
> print.data.frame( subset( sp.dli, id==603 )[,1:13], digits=3 )
```

	lex.id	tfi	tfr	tfD	tfr	lex.dur	lex.Cst	lex.Xst	id	from	to	time	distatpr
15739	603	0.00	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15740	603	0.10	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15741	603	0.20	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15742	603	0.30	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15743	603	0.40	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15744	603	0.50	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15745	603	0.60	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15746	603	0.70	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15747	603	0.80	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15748	603	0.90	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15749	603	1.00	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15750	603	1.10	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15751	603	1.20	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15752	603	1.30	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15753	603	1.40	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15754	603	1.50	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15755	603	1.60	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15756	603	1.70	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15757	603	1.80	NA	NA	NA	0.10000	Rem	Rem	603	0	2	1.90	1
15758	603	1.90	NA	NA	NA	0.00365	Rel	Rel	603	0	2	1.90	1
15759	603	1.90	0.0000	NA	NA	0.09635	Rel	Rel	603	2	4	2.79	1
15760	603	2.00	0.0963	NA	NA	0.10000	Rel	Rel	603	2	4	2.79	1
15761	603	2.10	0.1963	NA	NA	0.10000	Rel	Rel	603	2	4	2.79	1
15762	603	2.20	0.2963	NA	NA	0.10000	Rel	Rel	603	2	4	2.79	1
15763	603	2.30	0.3963	NA	NA	0.10000	Rel	Rel	603	2	4	2.79	1
15764	603	2.40	0.4963	NA	NA	0.10000	Rel	Rel	603	2	4	2.79	1
15765	603	2.50	0.5963	NA	NA	0.10000	Rel	Rel	603	2	4	2.79	1
15766	603	2.60	0.6963	NA	NA	0.10000	Rel	Rel	603	2	4	2.79	1
15767	603	2.70	0.7963	NA	NA	0.08980	Rel	DLI	603	2	4	2.79	1
15768	603	2.79	0.8862	0.0000	NA	0.01020	DLI	DLI	603	4	6	3.95	1
15769	603	2.80	0.8963	0.0102	NA	0.10000	DLI	DLI	603	4	6	3.95	1
15770	603	2.90	0.9963	0.1102	NA	0.10000	DLI	DLI	603	4	6	3.95	1
15771	603	3.00	1.0963	0.2102	NA	0.10000	DLI	DLI	603	4	6	3.95	1
15772	603	3.10	1.1963	0.3102	NA	0.10000	DLI	DLI	603	4	6	3.95	1
15773	603	3.20	1.2963	0.4102	NA	0.10000	DLI	DLI	603	4	6	3.95	1
15774	603	3.30	1.3963	0.5102	NA	0.10000	DLI	DLI	603	4	6	3.95	1
15775	603	3.40	1.4963	0.6102	NA	0.10000	DLI	DLI	603	4	6	3.95	1
15776	603	3.50	1.5963	0.7102	NA	0.10000	DLI	DLI	603	4	6	3.95	1
15777	603	3.60	1.6963	0.8102	NA	0.10000	DLI	DLI	603	4	6	3.95	1
15778	603	3.70	1.7963	0.9102	NA	0.10000	DLI	DLI	603	4	6	3.95	1
15779	603	3.80	1.8963	1.0102	NA	0.10000	DLI	DLI	603	4	6	3.95	1
15780	603	3.90	1.9963	1.1102	NA	0.04906	DLI	Rem2	603	4	6	3.95	1
15781	603	3.95	2.0454	1.1593	0.0000	0.05094	Rem2	Rem2	603	6	7	8.88	1
15782	603	4.00	2.0963	1.2102	0.0509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15783	603	4.10	2.1963	1.3102	0.1509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15784	603	4.20	2.2963	1.4102	0.2509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15785	603	4.30	2.3963	1.5102	0.3509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15786	603	4.40	2.4963	1.6102	0.4509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15787	603	4.50	2.5963	1.7102	0.5509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15788	603	4.60	2.6963	1.8102	0.6509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15789	603	4.70	2.7963	1.9102	0.7509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15790	603	4.80	2.8963	2.0102	0.8509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15791	603	4.90	2.9963	2.1102	0.9509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15792	603	5.00	3.0963	2.2102	1.0509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15793	603	5.10	3.1963	2.3102	1.1509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15794	603	5.20	3.2963	2.4102	1.2509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15795	603	5.30	3.3963	2.5102	1.3509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15796	603	5.40	3.4963	2.6102	1.4509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15797	603	5.50	3.5963	2.7102	1.5509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15798	603	5.60	3.6963	2.8102	1.6509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15799	603	5.70	3.7963	2.9102	1.7509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15800	603	5.80	3.8963	3.0102	1.8509	0.10000	Rem2	Rem2	603	6	7	8.88	1
15801	603	5.90	3.9963	3.1102	1.9509	0.10000	Rem2	Rem2	603	6	7	8.88	1

```

15802 603 6.00 4.0963 3.2102 2.0509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15803 603 6.10 4.1963 3.3102 2.1509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15804 603 6.20 4.2963 3.4102 2.2509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15805 603 6.30 4.3963 3.5102 2.3509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15806 603 6.40 4.4963 3.6102 2.4509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15807 603 6.50 4.5963 3.7102 2.5509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15808 603 6.60 4.6963 3.8102 2.6509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15809 603 6.70 4.7963 3.9102 2.7509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15810 603 6.80 4.8963 4.0102 2.8509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15811 603 6.90 4.9963 4.1102 2.9509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15812 603 7.00 5.0963 4.2102 3.0509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15813 603 7.10 5.1963 4.3102 3.1509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15814 603 7.20 5.2963 4.4102 3.2509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15815 603 7.30 5.3963 4.5102 3.3509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15816 603 7.40 5.4963 4.6102 3.4509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15817 603 7.50 5.5963 4.7102 3.5509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15818 603 7.60 5.6963 4.8102 3.6509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15819 603 7.70 5.7963 4.9102 3.7509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15820 603 7.80 5.8963 5.0102 3.8509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15821 603 7.90 5.9963 5.1102 3.9509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15822 603 8.00 6.0963 5.2102 4.0509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15823 603 8.10 6.1963 5.3102 4.1509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15824 603 8.20 6.2963 5.4102 4.2509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15825 603 8.30 6.3963 5.5102 4.3509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15826 603 8.40 6.4963 5.6102 4.4509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15827 603 8.50 6.5963 5.7102 4.5509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15828 603 8.60 6.6963 5.8102 4.6509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15829 603 8.70 6.7963 5.9102 4.7509 0.10000 Rem2 Rem2 603 6 7 8.88 1
15830 603 8.80 6.8963 6.0102 4.8509 0.07990 Rem2 D/Rem2 603 6 7 8.88 1

```

```
> summary( sp.dli )
```

```
Transitions:
```

```

To
From Rem D/Rem Rel D/Rel DLI D/DLI Rem2 D/Rem2 Rel2 Records: Events: Risk time:
Rem 10356 100 123 0 0 0 0 0 0 10579 223 1042.59
Rel 0 0 2485 40 65 0 0 0 0 2590 105 246.98
DLI 0 0 0 0 931 10 44 0 0 985 54 92.18
Rem2 0 0 0 0 0 0 1933 2 4 1939 6 189.38
Sum 10356 100 2608 40 996 10 1977 2 4 16093 388 1571.13

```

```
Transitions:
```

```

To
From Persons:
Rem 304
Rel 123
DLI 65
Rem2 44
Sum 304

```

We observe that the split dataset contains the same amount of person-years and event in the appropriate states and transitions, only the number of records is larger. The point is that each interval now has a different value of the timescales (`tfi`, `tfr`, `tfD`, and `tfR`), so that these can be used as a covariates. In the first instance we shall only use `tfi`

This dataset can now be stacked, and subsetted as before to allow for analysis of the mortality rates; later we also extract the other part of the stacked dataset, referring to the transitions between disease states:

```

> ss.dli <- stack( sp.dli )
> m.dli <- subset( ss.dli, lex.Tr %in% levels(lex.Tr)[c(1,3,5,7)] )
> m.dli$lex.Tr <- factor( m.dli$lex.Tr )
> m.dli$Rst <- Relevel( m.dli$lex.Tr, list(Remis=c(1,4),Relapse=2:3) )
> with( m.dli, ftable( Rst, lex.Tr, lex.Fail, col.vars=3 ) )

```

```

lex.Fail FALSE TRUE
Rst      lex.Tr
Remis    Rem->D/Rem      10479  100
          Rel->D/Rel        0    0
          DLI->D/DLI        0    0
          Rem2->D/Rem2     1937   2
Relapse  Rem->D/Rem        0    0
          Rel->D/Rel     2550   40
          DLI->D/DLI      975   10
          Rem2->D/Rem2      0    0

```

We also inspect how the deaths are distributed over the intervals of time (since entry, *i.e.* first remission), albeit only for the first two years:

```

> YDtab <- xtabs( cbind(lex.dur,lex.Fail) ~ I(floor(tfi*10)/10) + Rst,
+               data=subset(m.dli,tfi<2.1) )
> dnam <- dimnames(YDtab)
> dnam[[3]] <- c("Y","D","rate")
> YDrate <- array( NA, dimnames=dnam, dim=sapply(dnam,length) )
> YDrate[,1:2] <- YDtab
> YDrate[,3] <- YDrate[,2]/YDrate[,1]*1000
> round( ftable( YDrate, row.vars=1 ), 1 )

```

	Rst	Remis		Relapse			
		Y	D	rate	Y	D	rate
I(floor(tfi * 10)/10)							
0		30.1	11.0	365.4	0.0	0.0	0.0
0.1		27.9	24.0	861.5	0.4	3.0	8377.5
0.2		24.4	20.0	818.3	1.0	1.0	988.2
0.3		22.1	5.0	226.2	2.1	3.0	1442.2
0.4		20.4	6.0	294.0	2.8	1.0	356.8
0.5		18.1	5.0	275.5	4.4	1.0	228.5
0.6		16.9	5.0	295.5	5.0	2.0	397.7
0.7		16.0	2.0	124.9	5.4	2.0	372.6
0.8		15.2	2.0	131.2	5.8	0.0	0.0
0.9		14.9	0.0	0.0	6.0	1.0	165.6
1		14.4	2.0	139.2	6.4	0.0	0.0
1.1		13.9	2.0	144.1	6.6	1.0	151.8
1.2		13.6	1.0	73.6	6.6	2.0	303.0
1.3		13.7	1.0	73.0	6.2	2.0	322.4
1.4		13.4	0.0	0.0	6.1	1.0	163.4
1.5		13.1	0.0	0.0	6.3	1.0	159.7
1.6		13.1	0.0	0.0	6.0	1.0	166.5
1.7		13.0	0.0	0.0	5.7	1.0	174.8
1.8		12.8	0.0	0.0	5.7	1.0	175.3
1.9		12.5	1.0	80.2	5.8	0.0	0.0
2		12.2	0.0	0.0	5.7	1.0	174.0

We see that there is a very large mortality in the “Relapse” group in beginning, essentially an immediate death after very early relapse (albeit based only on a very few cases).

We use natural splines with knots that are located at 0, at the quintiles and at the 95th percentile of the death times:

```

> ( m.kn <- with( subset( m.dli, lex.Fail ),
+               c(0,quantile( tfi+lex.dur, probs=c(1:4/5,0.95) )) ) )

```

	20%	40%	60%	80%	95%
0.0000000	0.1781533	0.3484463	0.8011891	2.6473747	9.1250021

We will use natural splines that are generated by the command `ns` from the `splines` package, but it is a bit clumsy, so we use the wrapper `Ns` from the `Epi` package:

```
> Ns
```

```

function( x, df = NULL, knots = NULL, intercept = FALSE, Boundary.knots=NULL )
{
  if( !is.null(df) ) ns( x, df=df )
  else
  {
    if( is.null( Boundary.knots ) )
    {
      if( !is.null( knots ) )
      {
        knots <- sort( unique( knots ) )
        ok <- c(1,length(knots))
        Boundary.knots <- knots[ok]
        knots <- knots[-ok]
      }
    }
    ns( x, knots=knots, intercept=intercept, Boundary.knots=Boundary.knots )
  }
}
<environment: namespace:Epi>

```

We can now model the mortality rates as in the Cox-model, but now with an explicit parametric form of the underlying mortality:

```

> m0 <- glm( lex.Fail ~ Ns( tfi, knots=m.kn ) + lex.Tr,
+           family = poisson, offset=log(lex.dur), data=m.dli )
> summary( m0 )

```

Call:

```

glm(formula = lex.Fail ~ Ns(tfi, knots = m.kn) + lex.Tr, family = poisson,
    data = m.dli, offset = log(lex.dur))

```

Deviance Residuals:

	Min	1Q	Median	3Q	Max
	-0.7317	-0.1293	-0.0778	-0.0638	4.6694

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.7849	0.2495	-3.145	0.001658
Ns(tfi, knots = m.kn)1	-1.1817	0.3804	-3.106	0.001893
Ns(tfi, knots = m.kn)2	-2.4641	0.4505	-5.470	4.51e-08
Ns(tfi, knots = m.kn)3	-3.2246	0.4081	-7.901	2.77e-15
Ns(tfi, knots = m.kn)4	-2.1643	0.6271	-3.451	0.000558
Ns(tfi, knots = m.kn)5	-3.5468	0.2822	-12.569	< 2e-16
lex.TrRel->D/Rel	1.2551	0.2104	5.967	2.42e-09
lex.TrDLI->D/DLI	1.1410	0.3602	3.167	0.001539
lex.TrRem2->D/Rem2	-0.8898	0.7316	-1.216	0.223901

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 1689.7 on 16092 degrees of freedom
 Residual deviance: 1425.7 on 16084 degrees of freedom
 AIC: 1747.7

Number of Fisher Scoring iterations: 8

```

> round(ci.lin( m0, E=T ),3)

```

	Estimate	StdErr	z	P	exp(Est.)	2.5%	97.5%
(Intercept)	-0.785	0.250	-3.145	0.002	0.456	0.280	0.744
Ns(tfi, knots = m.kn)1	-1.182	0.380	-3.106	0.002	0.307	0.146	0.647
Ns(tfi, knots = m.kn)2	-2.464	0.451	-5.470	0.000	0.085	0.035	0.206
Ns(tfi, knots = m.kn)3	-3.225	0.408	-7.901	0.000	0.040	0.018	0.089
Ns(tfi, knots = m.kn)4	-2.164	0.627	-3.451	0.001	0.115	0.034	0.393
Ns(tfi, knots = m.kn)5	-3.547	0.282	-12.569	0.000	0.029	0.017	0.050
lex.TrRel->D/Rel	1.255	0.210	5.967	0.000	3.508	2.323	5.298
lex.TrDLI->D/DLI	1.141	0.360	3.167	0.002	3.130	1.545	6.341
lex.TrRem2->D/Rem2	-0.890	0.732	-1.216	0.224	0.411	0.098	1.723

We see that the value of the regression parameters and their s.e. are virtually the same as from the Cox-model:

```
> round(cbind( ci.lin( m0, subset="->" )[,1:2],
+             ci.lin( c0             )[,1:2] ), 4 )
      Estimate StdErr Estimate StdErr
lex.TrRel->D/Rel    1.2551 0.2104    1.2396 0.2103
lex.TrDLI->D/DLI    1.1410 0.3602    1.1652 0.3604
lex.TrRem2->D/Rem2 -0.8898 0.7316   -0.9073 0.7320
> round(cbind( ci.lin( m0, subset="->" )[,1:2]/
+             ci.lin( c0             )[,1:2] ), 4 )
      Estimate StdErr
lex.TrRel->D/Rel    1.0125 1.0003
lex.TrDLI->D/DLI    0.9792 0.9995
lex.TrRem2->D/Rem2  0.9808 0.9995
```

We make the same model reduction as before and make a similar test:

```
> m1 <- update( m0, . ~ . - lex.Tr + Rst )
> anova( m0, m1, test="Chisq" )
Analysis of Deviance Table

Model 1: lex.Fail ~ Ns(tfi, knots = m.kn) + lex.Tr
Model 2: lex.Fail ~ Ns(tfi, knots = m.kn) + Rst
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1     16084     1425.7
2     16086     1427.7 -2  -1.9935  0.3691
```

with pretty much the same result. But with the Poisson model we can easily make a likelihood-ratio tests for non-proportionality, both in the case with 4 different transitions, and in the case where we have assumed them to be pairwise equivalent:

```
> m0i <- update( m0, . ~ . + Ns( tfi, knots=m.kn ):lex.Tr )
> m1i <- update( m1, . ~ . + Ns( tfi, knots=m.kn ):Rst )
> anova( m0, m0i, test="Chisq" )
Analysis of Deviance Table

Model 1: lex.Fail ~ Ns(tfi, knots = m.kn) + lex.Tr
Model 2: lex.Fail ~ Ns(tfi, knots = m.kn) + lex.Tr + Ns(tfi, knots = m.kn):lex.Tr
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1     16084     1425.7
2     16070     1405.7 14  19.945  0.1319
> anova( m1, m1i, test="Chisq" )
Analysis of Deviance Table

Model 1: lex.Fail ~ Ns(tfi, knots = m.kn) + Rst
Model 2: lex.Fail ~ Ns(tfi, knots = m.kn) + Rst + Ns(tfi, knots = m.kn):Rst
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1     16086     1427.7
2     16081     1415.1  5   12.58  0.02764
```

It is clear that the test for proportional hazards between the 4 transitions to death is swamped by too many d.f. and that there actually is pretty clear evidence that the mortality rates from the remission states and from the relapsed states are not proportional (on the `tfi` scale). This type of analysis would not be straight-forward in a Cox-model.

Also we can test whether the reduction to two sets of mortality rates is OK in the stratified model. This is a formal test of whether the four different mortality rates can be reduced to two:


```
> anova( m0i, m1i, test="Chisq" )
Analysis of Deviance Table

Model 1: lex.Fail ~ Ns(tfi, knots = m.kn) + lex.Tr + Ns(tfi, knots = m.kn):lex.Tr
Model 2: lex.Fail ~ Ns(tfi, knots = m.kn) + Rst + Ns(tfi, knots = m.kn):Rst
  Resid. Df Resid. Dev  Df Deviance Pr(>Chi)
1      16070      1405.7
2      16081      1415.1 -11   -9.3579  0.5889
```

Thus, there is some evidence that there is non-proportionality between rates from the remission states and the relapse states, but not much evidence that the two sets of rates from remission states and the two sets of rates from relapse states are different. Therefore it is of interest to see how the underlying rates look in the two groups.

To this end we take a look at the parameters of the model:

```
> ci.lin( m1i )[,1:2]
              Estimate      StdErr
(Intercept) -0.8183893  0.2553555
Ns(tfi, knots = m.kn)1 -0.7188073  0.4141722
Ns(tfi, knots = m.kn)2 -2.5341692  0.5987644
Ns(tfi, knots = m.kn)3 -3.6711674  0.5887807
Ns(tfi, knots = m.kn)4 -2.6440625  0.6945684
Ns(tfi, knots = m.kn)5 -3.9173886  0.3773226
RstRelapse    6.5152164  1.9465422
Ns(tfi, knots = m.kn)1:RstRelapse -6.1354950  1.8893898
Ns(tfi, knots = m.kn)2:RstRelapse -5.1314819  2.1231917
Ns(tfi, knots = m.kn)3:RstRelapse -2.2057787  1.2012891
Ns(tfi, knots = m.kn)4:RstRelapse -10.0551098  4.3230728
Ns(tfi, knots = m.kn)5:RstRelapse -1.5407423  0.8546522
```

In order to show the rates we need to multiply the parameters by a matrix where each row are numbers to be multiplied to the parameter estimates to produce the estimated log-rates at a given point in time. This is set up using the same machinery of natural splines that was used in the model, but now not with the observed values of `tfi` as in the data, but with the values where we want the predictions made, *in casu* `pr.pt`:

```
> pr.pt <- seq(0,10,0.02)
> n.pt <- length( pr.pt )
> CM <- cbind( 1, Ns( pr.pt, knots=m.kn ) )
```

This is the matrix that we must multiply to the parameter vector (or subset of it) in order to get the log-mortality rates evaluated at the points in `pr.pt`. The function `ci.exp` exponentiates the results so that they are given as rates.

```
> Rem.Dead <- ci.exp( m1i, ctr.mat=cbind(CM,CM*0) )
> Rel.Dead <- ci.exp( m1i, ctr.mat=cbind(CM,CM) )

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> matplot( pr.pt, cbind( Rem.Dead, Rel.Dead )*100, log="y", ylim=c(1,400),
+         type="l", lty=1, lwd=c(3,1,1), las=1,
+         col=rep(cclr<-c("limegreen","red"),each=3),
+         ylab="Mortality rates per 100 PY", xlab="Time since entry" )
> text( c(10,10), 400*c(0.8,1), c("Remission","Relapse"), col=cclr,
+       adj=c(1,1) )
```

We can make it a bit more fancy by adding the RR between the two rates:

```

> RR.RmRl <- ci.exp( m1i, ctr.mat=cbind(CM*0,CM) )
> par( mar=c(3,4,1,4), mgp=c(3,1,0)/1.6 )
> matplot( pr.pt, cbind( Rem.Dead, Rel.Dead )*100, log="y", ylim=c(1,400),
+         type="l", lty=1, lwd=c(3,1,1),
+         col=rep(c("limegreen","red"),each=3),
+         ylab="Rate per 100 PY", xlab="Time since entry", yaxt="n" )
> abline( h=10 )
> matlines( pr.pt, RR.RmRl*10, type="l", lty=1, lwd=c(3,1,1), col="blue" )
> yt <- outer(c(1,2,5),c(1,10,100,1000),"*")
> axis( side=2, at=yt, labels=yt, las=1 )
> axis( side=4, at=yt, labels=yt/10, las=1 )
> mtext( "Rate ratio", side=4, line=2, col="blue" )

```

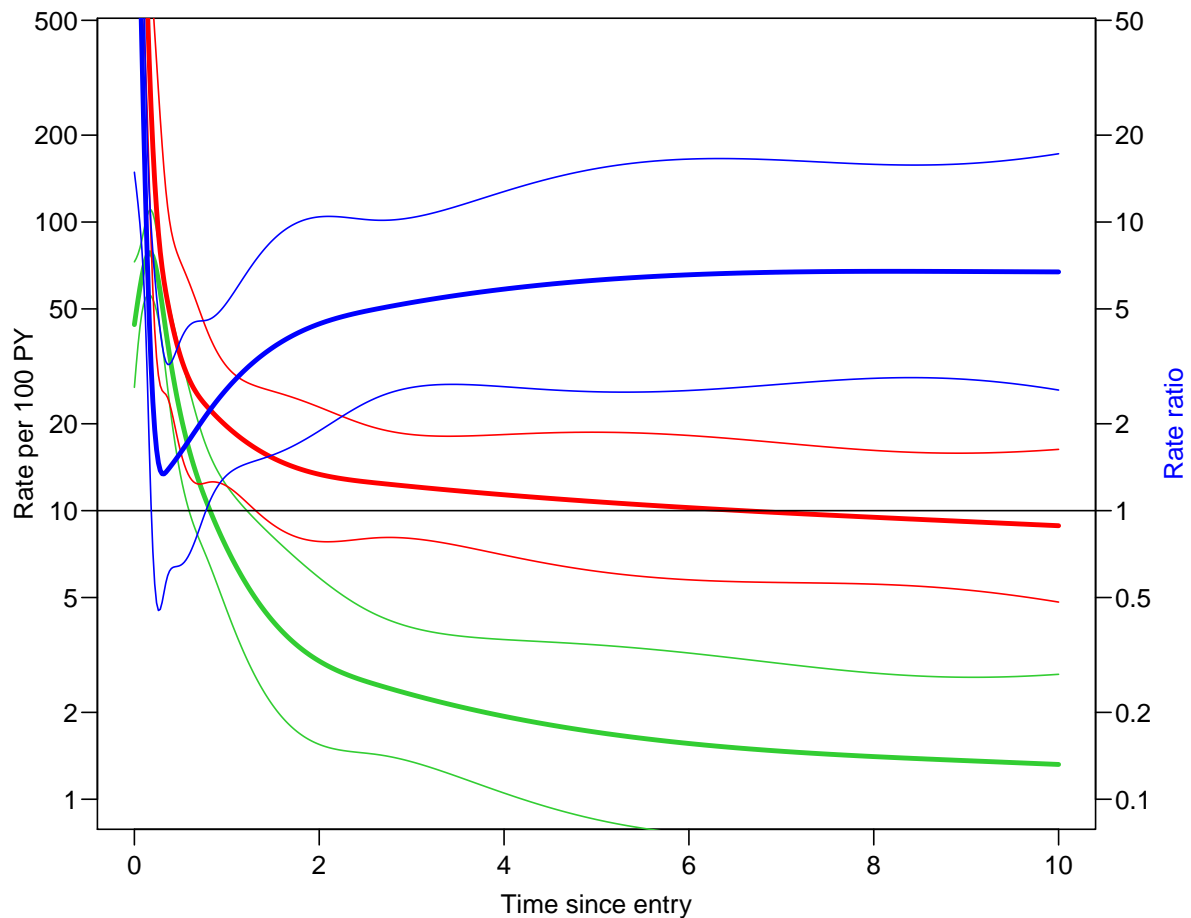


Figure 2: *Estimated baseline mortality rates from remission (green) and relapse (red), and the ratio of them (blue).*

2.2 Transitions through the disease states

For the non-mortality transition rates there is not much sense in having common rates, so we fit a separate rate for each.

However, we first explore how events are distributed along the timescale for the different transitions:

```
> str( ss.dli )
Classes 'stacked.Lexis' and 'data.frame':      32186 obs. of  19 variables:
 $ lex.id   : int  2 2 2 2 2 2 2 2 2 2 ...
 $ tfi     : num  0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 ...
 $ tfr     : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tfD     : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tfR     : num  NA NA NA NA NA NA NA NA NA NA ...
 $ lex.dur  : num  0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 ...
 $ lex.Cst  : Factor w/ 9 levels "Rem","D/Rem",...: 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Xst  : Factor w/ 9 levels "Rem","D/Rem",...: 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Tr   : Factor w/ 8 levels "Rem->D/Rem","Rem->Rel",...: 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Fail: logi  FALSE FALSE FALSE FALSE FALSE FALSE ...
 $ id      : int  2 2 2 2 2 2 2 2 2 2 ...
 $ from    : num  0 0 0 0 0 0 0 0 0 0 ...
 $ to      : num  0 0 0 0 0 0 0 0 0 0 ...
 $ time    : num  19.9 19.9 19.9 19.9 19.9 19.9 ...
 $ distatpr: int  1 1 1 1 1 1 1 1 1 1 ...
 $ ti      : num  0 0 0 0 0 0 0 0 0 0 ...
 $ tr      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tD      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ tR      : num  NA NA NA NA NA NA NA NA NA NA ...
 - attr(*, "breaks")=List of 4
 ..$ tfi: num  0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 ...
 ..$ tfr: NULL
 ..$ tfD: NULL
 ..$ tfR: NULL
 - attr(*, "time.scales")= chr  "tfi" "tfr" "tfD" "tfR"

> with( subset( ss.dli, lex.Fail & lex.Tr %in% levels(lex.Tr)[-c(1,3,5,7)] ),
+       dotchart( tfi+lex.dur, groups=factor(lex.Tr), pch=16, cex=0.8) )
```

From figure 3 it seems that there is a reasonable distribution of event times for all 4 types of transitions, so we use the same set of knots for all transitions:

```
> p.dli <- subset( ss.dli, lex.Tr %in% levels(lex.Tr)[-c(1,3,5,7)] )
> p.dli$lex.Tr <- factor( p.dli$lex.Tr )
> ( p.kn <-with( subset( p.dli, lex.Fail ),
+              c(0,quantile( tfi+lex.dur, probs=c(1:2/3,0.95) )) ) )
              33.33333% 66.66667%    95%
0.0000000 0.7526866 2.0012255 7.0256809
```

A quick glance at figure 1, however shows that there is virtually no information to estimate the transition from Rem2→Rel2, so we pool this transition with the transition Rem→Rel:

```
> p.dli$lex.Tr <- Relevel( p.dli$lex.Tr, list("Rem->Rel"=c(1,4), 2, 3 ) )
```

With the new set of knots defined we now fit separate transition rates for the four remaining transitions (modeled as 3). Note that we use `intercept=TRUE` to include the intercept with the natural spline:

```
> p2 <- glm( lex.Fail ~ Ns( tfi, knots=p.kn, intercept=TRUE ):lex.Tr -1 ,
+           family = poisson, offset=log(lex.dur), data=p.dli )
> summary( p2 )
```

```

Call:
glm(formula = lex.Fail ~ Ns(tfi, knots = p.kn, intercept = TRUE):lex.Tr -
  1, family = poisson, data = p.dli, offset = log(lex.dur))

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.4456  -0.2408  -0.0973  -0.0561   4.3088

Coefficients:
                                                    Estimate Std. Error z value
Ns(tfi, knots = p.kn, intercept = TRUE)1:lex.TrRem->Rel  -0.7465     0.2330  -3.203
Ns(tfi, knots = p.kn, intercept = TRUE)2:lex.TrRem->Rel  -3.0261     0.3748  -8.074
Ns(tfi, knots = p.kn, intercept = TRUE)3:lex.TrRem->Rel  -5.1797     0.3317 -15.616
Ns(tfi, knots = p.kn, intercept = TRUE)4:lex.TrRem->Rel  -3.3975     0.2876 -11.814
Ns(tfi, knots = p.kn, intercept = TRUE)1:lex.TrRel->DLI  -0.2264     0.3827  -0.592
Ns(tfi, knots = p.kn, intercept = TRUE)2:lex.TrRel->DLI  -1.3893     0.4356  -3.189
Ns(tfi, knots = p.kn, intercept = TRUE)3:lex.TrRel->DLI  -2.8973     0.7826  -3.702
Ns(tfi, knots = p.kn, intercept = TRUE)4:lex.TrRel->DLI  -1.9956     0.4445  -4.489
Ns(tfi, knots = p.kn, intercept = TRUE)1:lex.TrDLI->Rem2  -0.3395     0.6610  -0.514
Ns(tfi, knots = p.kn, intercept = TRUE)2:lex.TrDLI->Rem2  -0.9457     0.8024  -1.179
Ns(tfi, knots = p.kn, intercept = TRUE)3:lex.TrDLI->Rem2  -0.8512     1.9127  -0.445
Ns(tfi, knots = p.kn, intercept = TRUE)4:lex.TrDLI->Rem2  -1.1802     1.0326  -1.143
                                                    Pr(>|z|)
Ns(tfi, knots = p.kn, intercept = TRUE)1:lex.TrRem->Rel  0.001359
Ns(tfi, knots = p.kn, intercept = TRUE)2:lex.TrRem->Rel  6.81e-16
Ns(tfi, knots = p.kn, intercept = TRUE)3:lex.TrRem->Rel  < 2e-16
Ns(tfi, knots = p.kn, intercept = TRUE)4:lex.TrRem->Rel  < 2e-16
Ns(tfi, knots = p.kn, intercept = TRUE)1:lex.TrRel->DLI  0.554157
Ns(tfi, knots = p.kn, intercept = TRUE)2:lex.TrRel->DLI  0.001427
Ns(tfi, knots = p.kn, intercept = TRUE)3:lex.TrRel->DLI  0.000214
Ns(tfi, knots = p.kn, intercept = TRUE)4:lex.TrRel->DLI  7.14e-06
Ns(tfi, knots = p.kn, intercept = TRUE)1:lex.TrDLI->Rem2  0.607530
Ns(tfi, knots = p.kn, intercept = TRUE)2:lex.TrDLI->Rem2  0.238595
Ns(tfi, knots = p.kn, intercept = TRUE)3:lex.TrDLI->Rem2  0.656285

```

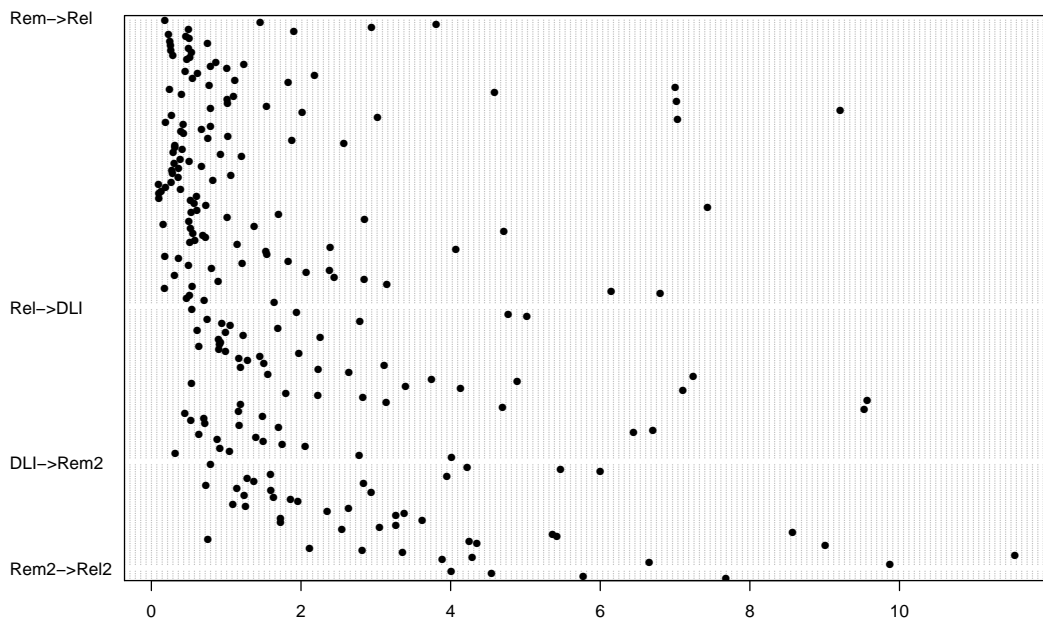


Figure 3: *Distribution of transition times for the non-death events.*

```

Ns(tfi, knots = p.kn, intercept = TRUE)4:lex.TrDLI->Rem2 0.253049

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 4250.4 on 16093 degrees of freedom
Residual deviance: 2175.4 on 16081 degrees of freedom
AIC: 2671.4

Number of Fisher Scoring iterations: 9
> round(ci.exp( p2, Exp=FALSE ), 2 )

```

	Estimate	2.5%	97.5%
Ns(tfi, knots = p.kn, intercept = TRUE)1:lex.TrRem->Rel	-0.75	-1.20	-0.29
Ns(tfi, knots = p.kn, intercept = TRUE)2:lex.TrRem->Rel	-3.03	-3.76	-2.29
Ns(tfi, knots = p.kn, intercept = TRUE)3:lex.TrRem->Rel	-5.18	-5.83	-4.53
Ns(tfi, knots = p.kn, intercept = TRUE)4:lex.TrRem->Rel	-3.40	-3.96	-2.83
Ns(tfi, knots = p.kn, intercept = TRUE)1:lex.TrRel->DLI	-0.23	-0.98	0.52
Ns(tfi, knots = p.kn, intercept = TRUE)2:lex.TrRel->DLI	-1.39	-2.24	-0.54
Ns(tfi, knots = p.kn, intercept = TRUE)3:lex.TrRel->DLI	-2.90	-4.43	-1.36
Ns(tfi, knots = p.kn, intercept = TRUE)4:lex.TrRel->DLI	-2.00	-2.87	-1.12
Ns(tfi, knots = p.kn, intercept = TRUE)1:lex.TrDLI->Rem2	-0.34	-1.63	0.96
Ns(tfi, knots = p.kn, intercept = TRUE)2:lex.TrDLI->Rem2	-0.95	-2.52	0.63
Ns(tfi, knots = p.kn, intercept = TRUE)3:lex.TrDLI->Rem2	-0.85	-4.60	2.90
Ns(tfi, knots = p.kn, intercept = TRUE)4:lex.TrDLI->Rem2	-1.18	-3.20	0.84

We now apply the same machinery as before, and construct a contrast matrix to extract the transition rates:

```

> CP <- Ns( pr.pt, knots=p.kn, intercept=TRUE )
> Rem.Rel <- ci.exp( p2, subset="TrRem", ctr.mat=CP )
> Rel.DLI <- ci.exp( p2, subset="TrRel", ctr.mat=CP )
> DLI.Rem <- ci.exp( p2, subset="TrDLI", ctr.mat=CP )

```

and we can plot these three *progression* rates together:

```

> par( mar=c(3,4,1,4), mgp=c(3,1,0)/1.6 )
> matplot( pr.pt, cbind(Rem.Rel,Rel.DLI,DLI.Rem)*100, log="y", ylim=c(1,500),
+         type="l", lty=1, lwd=c(3,1,1),
+         col=rep(c("limegreen","red","blue"),each=3),
+         ylab="Progression rate per 100 PY", xlab="Time since entry" )
> par(font=2)
> legend( "topright", legend=c("Remission > Relapse",
+                             "Relapse > DLI",
+                             "DLI > Remission"), bty="n",
+         text.col=c("limegreen","red","blue"), xjust=1 )

```

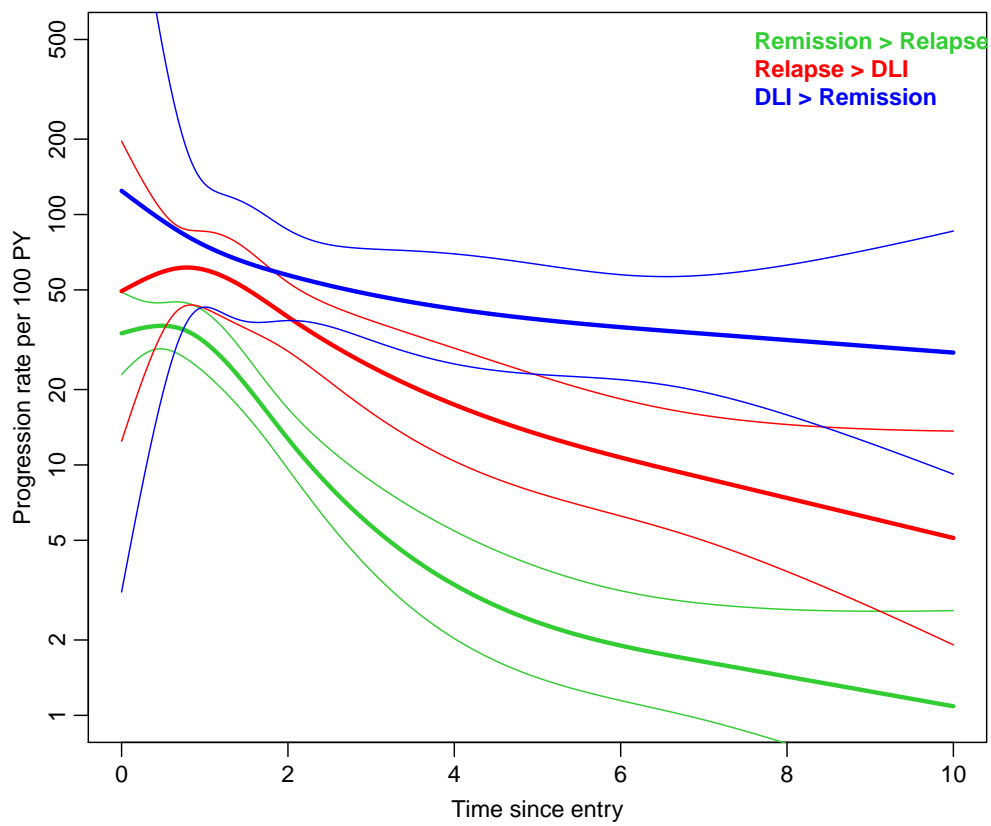


Figure 4: *Estimated disease progression rates.*

3 State occupancy probability

In the paper by Allignol *et al.*[1], the probabilities are referred to as transition probabilities. But since the authors only ever consider transition probabilities from time 0, they are just probabilities of being in a particular state at some time (given of course that the person starts in the study at time 0).

The progression rates as shown are difficult to interpret, so we will instead have a look at how state occupancy looks. Also to be able to show how the overall remission probability evolves, that is how the probability of being in one of the states “Rem” and “Rem2” changes with time since entry into the study.

We can compute the probability of being in a particular state at various times by multiplying the initial state distribution vector (in this case $(1, 0, 0, 0, 0, 0, 0, 0, 0)$), by multiplying it by the transition matrix, that is the matrix of transition probabilities between states. Now this varies by time, because the transition rates vary. But we have computed the transition rates at narrowly spaced intervals, so we can make a very good approximation of the transition probabilities by computing them under the assumption of constant rates in these small intervals. Using `unique` demonstrates that differences are never reliable in computing:

```
> pr.pt[1:5]
[1] 0.00 0.02 0.04 0.06 0.08
> unique( diff(pr.pt) )
[1] 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02
> ( il <- mean( diff(pr.pt) ) )
[1] 0.02
```

What needs to be done now is to set up a structure (array) with the transition probability matrices as slices and the third dimension being the times in `pr.pt`.

First we fetch the state names from the `Lexis` object:

```
> states <- levels( dli$lex.Cst )
> dnam <- list(From=states, To=states, time=pr.pt )
> AR <- array( 0, dimnames=dnam, dim=sapply(dnam,length) )
> str( AR )
num [1:9, 1:9, 1:501] 0 0 0 0 0 0 0 0 0 0 ...
- attr(*, "dimnames")=List of 3
..$ From: chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
..$ To : chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
..$ time: chr [1:501] "0" "0.02" "0.04" "0.06" ...
```

Then we fill the array `AR` with the rates for the actually existing transitions, and from these later compute the one-step transition probabilities in `AP`:

```
> AR["Rem" , "D/Rem" , ] <- Rem.Dead[,1]
> AR["Rem2", "D/Rem2", ] <- Rem.Dead[,1]
> AR["Rel" , "D/Rel" , ] <- Rel.Dead[,1]
> AR["DLI" , "D/DLI" , ] <- Rel.Dead[,1]
> AR["Rem" , "Rel" , ] <- Rem.Rel[,1]
> AR["Rem2", "Rel2" , ] <- Rem.Rel[,1]
> AR["Rel" , "DLI" , ] <- Rel.DLI[,1]
> AR["DLI" , "Rem2" , ] <- DLI.Rem[,1]
```



```

D/Rem    0.0000 1.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000
Rel      0.0000 0.0000 0.9843 0.0038 0.0119 0.0000 0.0000 0.0000 0.0000
D/Rel    0.0000 0.0000 0.0000 1.0000 0.0000 0.0000 0.0000 0.0000 0.0000
DLI      0.0000 0.0000 0.0000 0.0000 0.9814 0.0038 0.0148 0.0000 0.0000
D/DLI    0.0000 0.0000 0.0000 0.0000 0.0000 1.0000 0.0000 0.0000 0.0000
Rem2     0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.9925 0.0014 0.0061
D/Rem2   0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 1.0000 0.0000
Rel2     0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 1.0000

```

Each of the slices of the array `AP` is a matrix of transition probabilities.

Suppose the initial state distribution is π_0 , in this case a vector of length 9:
 $\pi_0 = (1, 0, 0, 0, 0, 0, 0, 0, 0)$. The probability distribution after one step is then $\pi_1 = \pi_0 A_1$, where A_1 is the transition matrix for the first interval. After two steps it is $\pi_1 A_2$ and so forth.

So now we set up an array to store the state-distribution at different times; it has the same structure as the `SI` array:

```

> pi0 <- c(1,rep(0,8))
> ST <- SI*0
> ST[,1] <- pi0 %*% AP[,1]
> for( i in 2:dim(ST)[2] ) ST[,i] <- ST[,i-1] %*% AP[,i]
> str( ST )
  num [1:9, 1:501] 0.98459 0.00875 0.00666 0 0 ...
 - attr(*, "dimnames")=List of 2
  ..$ From: chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
  ..$ time: chr [1:501] "0" "0.02" "0.04" "0.06" ...
> round(t(ST[,1:10]),3)
      From
time   Rem D/Rem  Rel D/Rel  DLI D/DLI Rem2 D/Rem2 Rel2
0      0.985 0.009 0.007 0.000 0.000 0 0 0 0
0.02   0.968 0.018 0.007 0.006 0.000 0 0 0 0
0.04   0.952 0.029 0.008 0.012 0.000 0 0 0 0
0.06   0.934 0.040 0.009 0.017 0.000 0 0 0 0
0.08   0.916 0.052 0.012 0.021 0.000 0 0 0 0
0.1    0.897 0.064 0.015 0.024 0.000 0 0 0 0
0.12   0.878 0.077 0.018 0.026 0.000 0 0 0 0
0.14   0.859 0.091 0.022 0.028 0.000 0 0 0 0
0.16   0.839 0.104 0.026 0.030 0.001 0 0 0 0
0.18   0.821 0.117 0.030 0.031 0.001 0 0 0 0

```

The estimated occupancy probabilities for each of the states can now easily be plotted:

```

> matplot( pr.pt, t(ST)[-1], type="l", ylim=c(0,0.5), las=1,
+         lty=1, lwd=2, col=rainbow(8),
+         xlab="Time since 1st remission", ylab="Fraction of patients" )
> legend( "topleft", legend=rownames(ST)[-1],
+        bty="n", lty=1, lwd=2, col=rainbow(8),
+        ncol=1 )

```

Once we have that, we can plot the more easily readable *cumulative* state-occupancies, by cumulating over the 1st dimension of `ST` (that is a loop over dimension 2), which in the case of using `cumsum` returns a vector, and so adds a dimension equal to the length of this as the *first* dimension of the result:

```
> cST <- apply(ST,2,cumsum)
```

This could easily be plotted using *e.g.*:

```
> matplot( pr.pt, t(cST), type="l", lty=1, lwd=2 )
```

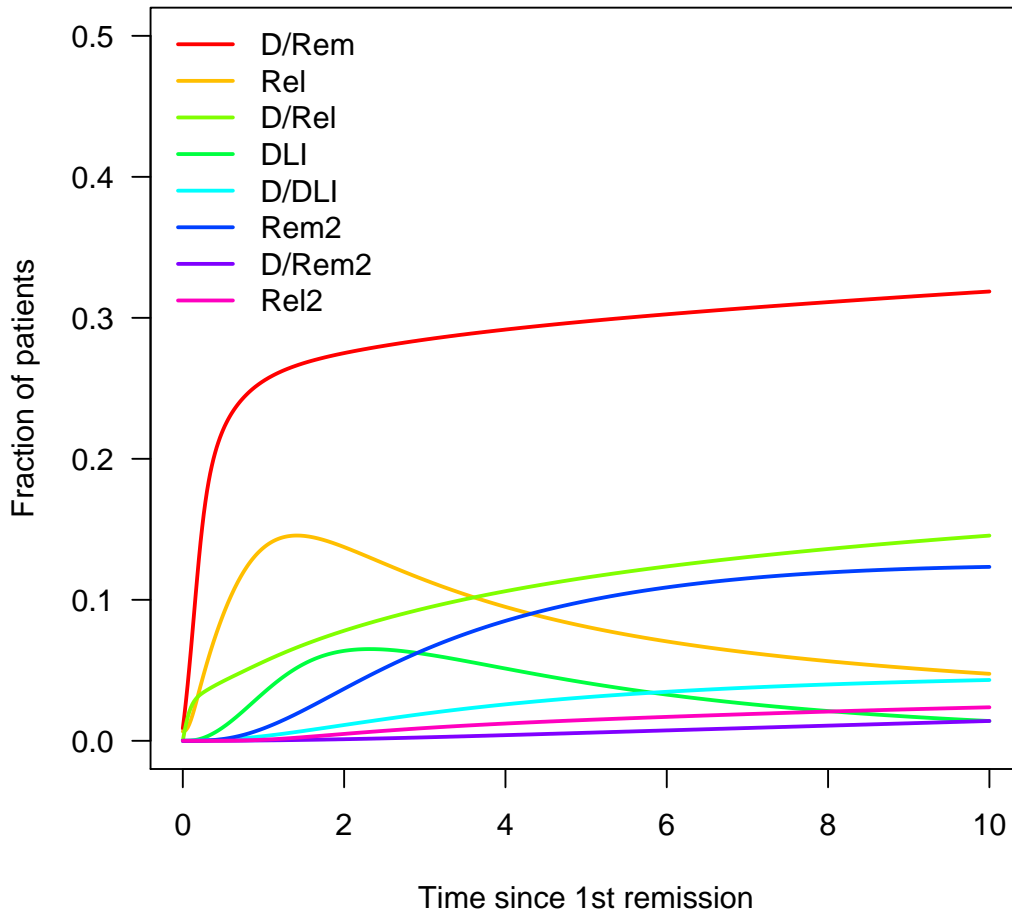


Figure 5: *Estimated state occupancy probabilities for each state.*

It would however be nicer to be able to show the states in an arbitrary order; but this is easily packed into one command, by defining a vector `perm` which is a permutation of the levels:

```
> perm <- c(1,3,5,7,9,2,4,6,8)
> dimnames(ST)[[1]][perm]
  [1] "Rem"    "Rel"    "DLI"    "Rem2"    "Rel2"    "D/Rem"  "D/Rel"  "D/DLI"  "D/Rem2"
> matplot( pr.pt, t(apply(ST[perm,],2,cumsum)), type="l", lty=1, lwd=2 )
```

This is not extremely informative, because it is the space between the lines that is of interest. Moreover it would be relevant to be able to write the state-names at the ends, for example:

```
> endpos <- cumsum(ST[perm,n.pt]) - ST[perm,n.pt]/2
> matplot( pr.pt, t(apply(ST[perm,],2,cumsum)),
+         type="l", lty=1, lwd=2, col=gray(c(0.6,0)[c(1,1,1,1,2,1,1,1,1)]),
+         xlim=c(0,11.5), ylim=c(0,1), yaxs="i" )
> text( 10.05, endpos, dimnames(ST)[[1]][perm], font=2, adj=0 )
```

Furthermore, if we want to color the areas between the curves, we just start from the top and color the area underneath each curve. We also make sure that there is place for the labels at the edges (although the algorithm for this is not complete yet). We put it all in a function with `perm` as an argument, to allow us to change the ordering of the states:

```
> state.occ <-
+ function( perm=1:n.st, line=NULL )
+ {
+   clr <- st.col[perm]
+   +
+   mindist <- 1/40
+   endpos <- cumsum(ST[perm,n.pt]) - ST[perm,n.pt]/2
+   minpos <- (1:n.st-0.5)*mindist
+   maxpos <- 1-rev(minpos)
+   endpos <- pmin( pmax( endpos, minpos ), maxpos )
+   +
+   stkcrv <- t(apply(ST[perm,],2,cumsum))
+   matplot( pr.pt, stkcrv,
+             type="l", lty=1, lwd=1, col="transparent",
+             xlim=c(0,11.5), ylim=c(0,1), yaxs="i", xaxs="i", bty="n",
+             xlab="Time since 1st remission", ylab="Fraction of patients" )
+   text( 10.05, endpos, dimnames(ST)[[1]][perm], font=2, adj=0, col=clr )
+   for( i in 9:1 )
+   + polygon( c( pr.pt, rev(pr.pt) ),
+             c( stkcrv[,i], if(i>1) rev(stkcrv[,i-1]) else rep(0,n.pt) ),
+             col=clr[i], border=clr[i] )
+   + if( !is.null(line) )
+   + matlines( pr.pt, stkcrv[,line], type="l", lty=1, lwd=3, col="black" )
+ }
```

With this function in place we can make plots for different orderings of the states, but maintaining the colors for each state. Also note that we have grouped the “alive” states together, so we can sensibly show the survival curve, separating the alive from the dead:

```
> state.occ( perm=1:n.st )

> state.occ( perm=c(1,3,5,7,9,2,4,6,8), line=5 )
```

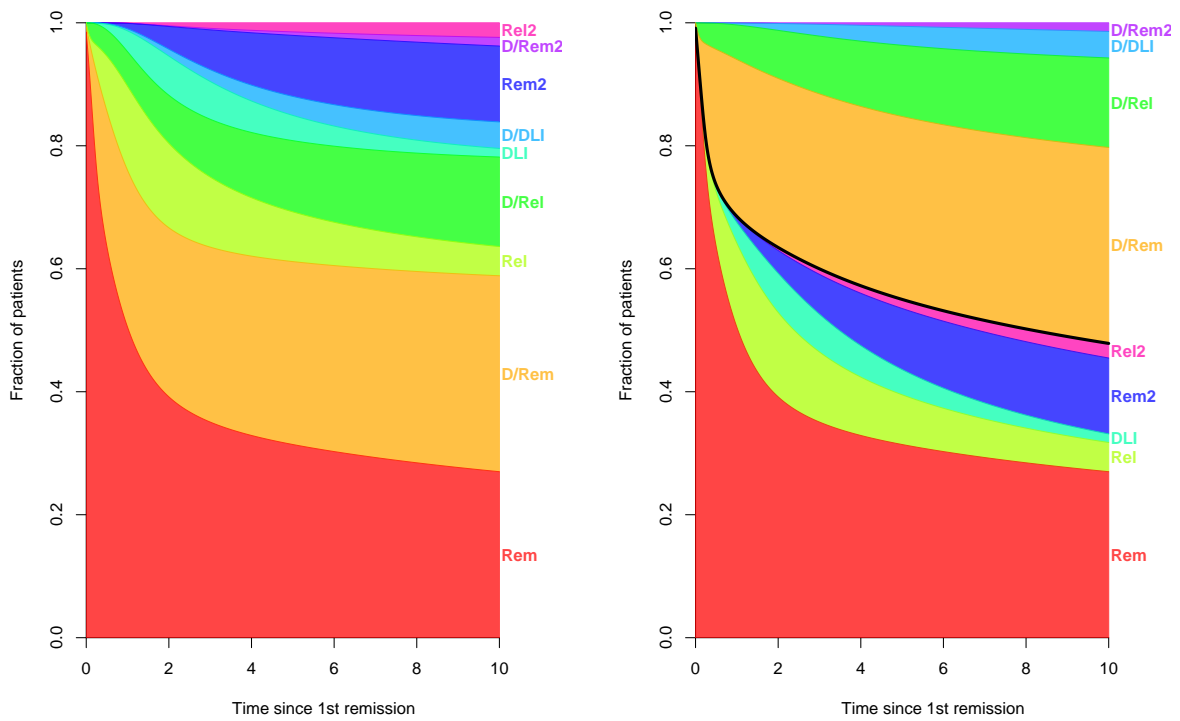


Figure 6: *Estimated state occupancy probabilities. The only difference is the ordering of the states. The black line in the rightmost display is the estimated survival curve.*

3.1 Confidence interval for state occupancies

The uncertainty of these cumulative probabilities are not easily assessed, because they are non-linear functions of the parameters of the glms used to fit the data.

The natural thing to do would therefore be to simulate in some way. Either by bootstrapping the original data and redo the entire analysis for each bootstrap sample, thereby giving a sample from the “posterior” distribution of the relevant quantities.

Or (slightly simpler) by simulation from an assumed normal distribution of the parameter estimates in the model. The latter is achieved by using the `sample=` argument to `ci.lin`, which when set to a number takes a sample from a multivariate normal distribution with mean equal to the estimated parameters and variance-covariance matrix equal to the estimated.

In order for this to work we should wrap all the previous stuff up in a couple of functions that does the work in suitable bits:

- Extract the transition rates and stuff them in a structure — `get.rates`
- Transform the transition matrices to probabilities
- Draw the curves (areas) in color and superpose them with confidence intervals.

When drawing a sample from the posterior we use the argument `sample` to `ci.lin`, that draws a sample from a multivariate normal with mean equal to the parameter estimates and variance equal to the estimated variance-covariance matrix, and transforms each sample by the supplied contrast matrix:

```
> get.rates <- function( N=10 )
+ {
+   Rem.Dead <- ci.lin( m1i,                ctr.mat=cbind(CM,CM*0), sample=N )
+   Rel.Dead <- ci.lin( m1i,                ctr.mat=cbind(CM,CM  ), sample=N )
+   Rem.Rel  <- ci.lin( p2 , subset="TrRem", ctr.mat=CP          , sample=N )
+   Rel.DLI  <- ci.lin( p2 , subset="TrRel", ctr.mat=CP          , sample=N )
+   DLI.Rem  <- ci.lin( p2 , subset="TrDLI", ctr.mat=CP          , sample=N )
+   states <- levels( dli$lex.Cst )
+   dnam <- list( From = states,
+                 To   = states,
+                 time  = pr.pt,
+                 sample = 1:N )
+   AR <- AP <- array( 0, dimnames=dnam, dim=sapply(dnam,length) )
+   AR["Rem" , "D/Rem" , ,] <- exp(Rem.Dead)
+   AR["Rem2" , "D/Rem2" , ,] <- exp(Rem.Dead)
+   AR["Rel" , "D/Rel" , ,] <- exp(Rel.Dead)
+   AR["DLI" , "D/DLI" , ,] <- exp(Rel.Dead)
+   AR["Rem" , "Rel" , ,] <- exp(Rem.Rel )
+   AR["Rem2" , "Rel2" , ,] <- exp(Rem.Rel )
+   AR["Rel" , "DLI" , ,] <- exp(Rel.DLI )
+   AR["DLI" , "Rem2" , ,] <- exp(DLI.Rem )
+   AR
+ }
> system.time( AR <- get.rates(1000) )
   user  system elapsed
  5.07    0.25    5.32
> str( AR )
num [1:9, 1:9, 1:501, 1:1000] 0 0 0 0 0 ...
- attr(*, "dimnames")=List of 4
 ..$ From : chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
 ..$ To   : chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
 ..$ time : chr [1:501] "0" "0.02" "0.04" "0.06" ...
 ..$ sample: chr [1:1000] "1" "2" "3" "4" ...
```

Thus in this general setup, we now have a function that produces an array classified by states \times states \times times \times samples, which contains (samples of) the transitions rates in the appropriate places in the resulting array.

Then we need a function that transforms this to a similar array of transition probabilities:

```
> trans.prob <-
+ function( AR )
+ {
+ # A matrix for transition probabilities:
+ AP <- AR * 0
+ # Compute the interval length for the give rates
+ il <- mean( diff( as.numeric( dimnames(AR)[[3]] ) ) )
+ # Sum of the Intensities out of each state
+ SI <- apply(AR,c(1,3,4),sum)
+ for( i in 1:dim(AR)[3] ) # Loop over times
+ for( j in 1:dim(AR)[4] ) # Loop over samples
+ {
+ AP[,i,j] <- AR[,i,j]/SI[,i,j] * (1-exp(-SI[,i,j]*il))
+ diag(AP[,i,j]) <- exp(-SI[,i,j]*il)
+ }
+ AP[is.na(AP)] <- 0
+ invisible( AP )
+ }
> system.time( AP <- trans.prob( AR ) )
      user  system elapsed
 93.24    0.78   94.33
```

We have now computed the transition probabilities for each time for each of the samples from the parameter estimates. So with this we can now compute the state occupancy probabilities:

```
> pi0 <- rep(1:0,c(1,n.st-1))
> ST <- AP[1,,]*0
> names( dimnames(ST) )[1] <- "State"
> str( ST )
  num [1:9, 1:501, 1:1000] 0 0 0 0 0 0 0 0 0 0 ...
 - attr(*, "dimnames")=List of 3
  ..$ State : chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
  ..$ time  : chr [1:501] "0" "0.02" "0.04" "0.06" ...
  ..$ sample: chr [1:1000] "1" "2" "3" "4" ...

> system.time(
+ for( j in 1:dim(ST)[3] )
+ {
+ ST[,1,j] <- pi0 %*% AP[,1,j]
+ for( i in 2:dim(ST)[2] ) ST[,i,j] <- ST[,i-1,j] %*% AP[,i,j]
+ }
+ )
      user  system elapsed
   7.24    0.00    7.32

> str( ST )
  num [1:9, 1:501, 1:1000] 0.98198 0.01083 0.00719 0 0 ...
 - attr(*, "dimnames")=List of 3
  ..$ State : chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
  ..$ time  : chr [1:501] "0" "0.02" "0.04" "0.06" ...
  ..$ sample: chr [1:1000] "1" "2" "3" "4" ...
```

By this time we have $N = 1000$ samples of occupancy probabilities as functions of time. If we want to plot these in a given order, we should *first* make the cumulative sums for each

of these over states as indicated by `perm`. Then we take for example the 5,50 and 95% quantiles, and use the median to demarcate the colored chunks, and the 5th and 95th percentiles to make shaded areas showing the (point-wise) 90% confidence for the probabilities.

This amounts to a slight modification and expansion of the `state.occ` function. We show the confidence bands by overlaying a transparent gray shade over the demarcations between the colors showing the occupancy probabilities. This is done using the color `rgb(1/9,1/9,1/9,1/9)`, which is a transparent light gray.

```
> state.occ.sim <-
+ function( perm = 1:n.st,
+           pct = c(5,95),
+           cicol = rgb(1/9,1/9,1/9,1/9),
+           line = NULL )
+ {
+   clr <- st.col[perm]
+   cST <- apply(ST[perm,,],2:3,cumsum)
+   cST <- apply(cST,1:2,quantile,probs=c(pct/100,0.5) )
+   mindist <- 1/40
+   endpos <- cST["50%",,n.pt] - diff(c(0,cST["50%",,n.pt]))/2
+   minpos <- (1:n.st-0.5)*mindist
+   maxpos <- 1-rev(minpos)
+   endpos <- pmin( pmax( endpos, minpos ), maxpos )
+
+   matplot( pr.pt, t(cST["50%",,]),
+            type="n", # lty=1, lwd=2, col=gray(c(0.6,0)[c(1,2,1,2,1,2,1,2,1)]),
+            xlim=c(0,11.5), ylim=c(0,1), yaxs="i", xaxs="i", bty="n",
+            xlab="Time since 1st remission", ylab="Fraction of patients" )
+   text( 10.05, endpos, dimnames(ST)[[1]][perm], font=2, adj=0, col=clr )
+   for( i in n.st:1 )
+   polygon( c( pr.pt, rev(pr.pt) ),
+            c( cST["50%",i,], if(i>1) rev(cST["50%",i-1,]) else rep(0,dim(cST)[3]) ),
+            col=clr[i], border=clr[i] )
+   for( i in n.st:1 )
+   polygon( c( pr.pt, rev(pr.pt) ),
+            c( cST[1,i,], rev(cST[2,i,]) ),
+            col=cicol, border=cicol )
+   if( !is.null(line) ) matlines( pr.pt, t(cST["50%",c(line,NA),]),
+                                 type="l", lty=1, lwd=3, col="black" )
+ }
```

With this function we can now plot various versions of the display, to show how the shaded confidence bands work:

```
> par(mar=c(3,3,1,1),mgp=c(3,1,0)/1.6,las=1)
> state.occ.sim( pct=c(5,95) )

> par(mar=c(3,3,1,1),mgp=c(3,1,0)/1.6,las=1)
> state.occ.sim( perm=c(1,3,5,7,9,2,4,6,8), pct=c(5,95), line=5 )
```

4 Probability of being in remission

Allignol *et al.*[1] produce a plot of the probability of being in remission, that is in either state “Rem” or “Rem2”. Incidentally this can easily be shown by changing the ordering in the above plot, as shown in figure ??:

```
> par(mar=c(3,3,1,1),mgp=c(3,1,0)/1.6,las=1)
> state.occ.sim( perm=c(1,7,3,5,9,4,6,8,2), pct=c(5,95), line=c(2,5) )
```

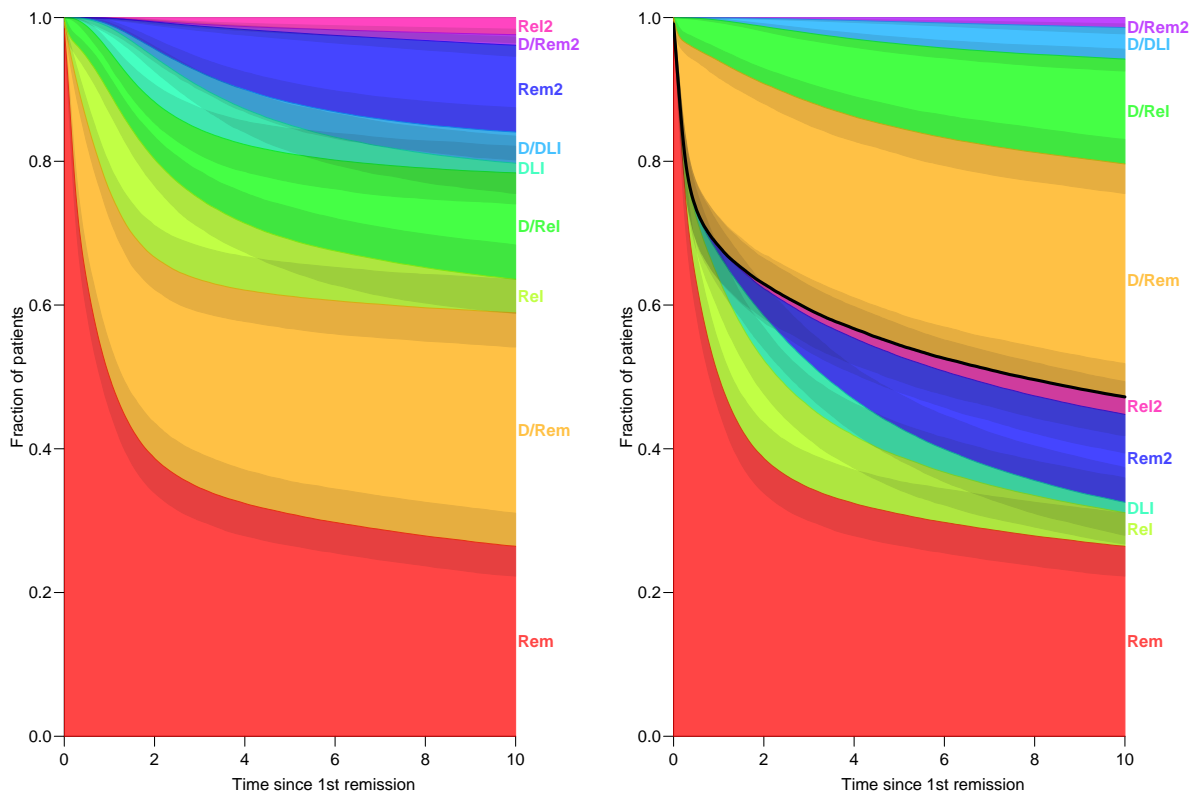


Figure 7: *Estimated state occupancy probabilities with 90% confidence bands based on a simulated sample of 1000 from the “posterior” distribution of the parameters from the Poisson model(s) for the transitions. The only difference is the ordering of the states; in the right hand panel the alive states are grouped together and the black line represents the survival curve.*

With our posterior sample we can also quite easily give a parametrically estimated counterpart of the 95% confidence interval to compare with the estimate from the `etm` package:

```
> CLFS <- apply( ST["Rem",,]+ST["Rem2",,], 1, quantile, probs=c(500,25,975)/1000 )
> str( CLFS )
 num [1:3, 1:501] 0.984 0.978 0.989 0.968 0.956 ...
- attr(*, "dimnames")=List of 2
 ..$ : chr [1:3] "50%" "2.5%" "97.5%"
 ..$ time: chr [1:501] "0" "0.02" "0.04" "0.06" ...
```

This can now be plotted and compared with the results using the `etm` package:

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> matplot( pr.pt, t(CLFS),
+         type="l", lty=1,lwd=c(3,1,1), col="black",
+         ylim=c(0,1),
+         ylab="P(CLFS)", xlab="Time since first remission" )
```

We do not show this figure, because we will overlay the estimated curve on the non-parametrically estimated curve that that can be computed from the `etm` package. This is essentially code from the paper [1], tidied a bit for readability:


```

> tra <- matrix(FALSE, 9, 9,
+               dimnames = list(as.character(0:8), as.character(0:8)))
> tra[1, 2:3] <- TRUE
> tra[3, 4:5] <- TRUE
> tra[5, 6:7] <- TRUE
> tra[7, 8:9] <- TRUE
> ### computation of the transition probabilities
> dli.etm <- etm(dli.data, as.character(0:8), tra, "cens", s = 0)
> str(dli.etm)
List of 12
 $ est      : num [1:9, 1:9, 1:536] 0.997 0 0 0 0 ...
 ..- attr(*, "dimnames")=List of 3
 .. ..$ : chr [1:9] "0" "1" "2" "3" ...
 .. ..$ : chr [1:9] "0" "1" "2" "3" ...
 .. ..$ : chr [1:536] "0.0329688509639716" "0.0555592940852114" "0.0593206943292609" "0.066534579
 $ cov      : num [1:81, 1:81, 1:536] 1.08e-05 0.00 0.00 0.00 0.00 ...
 ..- attr(*, "dimnames")=List of 3
 .. ..$ : chr [1:81, 1] "0 0" "1 0" "2 0" "3 0" ...
 .. ..$ : chr [1:81, 1] "0 0" "1 0" "2 0" "3 0" ...
 .. ..$ : chr [1:536] "0.0329688509639716" "0.0555592940852114" "0.0593206943292609" "0.066534579
 $ time     : num [1:536] 0.033 0.0556 0.0593 0.0665 0.0667 ...
 $ s       : num 0
 $ t       : num 21.1
 $ trans    : 'data.frame':      8 obs. of  2 variables:
 ..$ from: Factor w/ 4 levels "0","2","4","6": 1 1 2 2 3 3 4 4
 ..$ to  : Factor w/ 8 levels "1","2","3","4",..: 1 2 3 4 5 6 7 8
 $ state.names: chr [1:9] "0" "1" "2" "3" ...

```

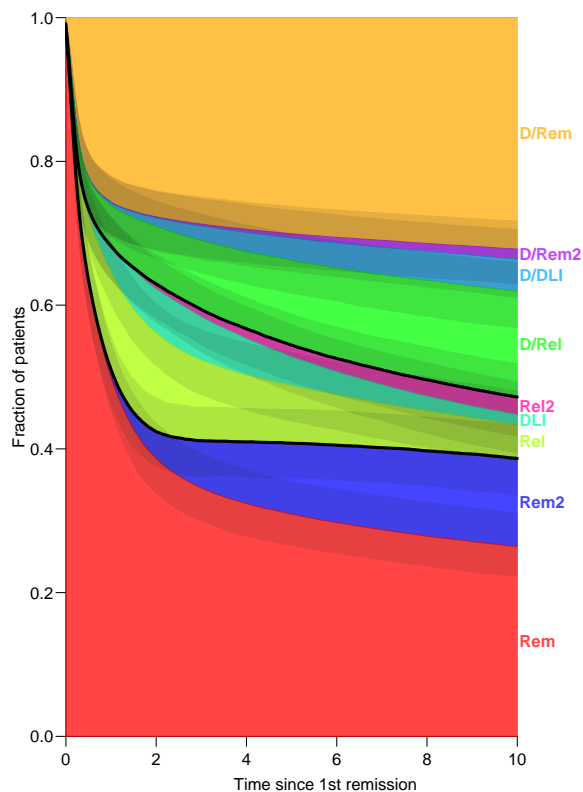


Figure 8: *Estimated state occupancy probabilities with 90% confidence bands based on a simulated sample of 1000 from the “posterior” distribution of the parameters from the Poisson model(s) for the transitions. The black lines represent the probability of being alive in remission and the probability of being alive at all. The only difference to figure 7 is the ordering of the states.*

```

$ cens.name : chr "cens"
$ n.risk     : int [1:536, 1:4] 304 303 302 301 300 299 298 297 296 295 ...
..- attr(*, "dimnames")=List of 2
.. ..$ : NULL
.. ..$ : chr [1:4] "0" "2" "4" "6"
$ n.event    : int [1:9, 1:9, 1:536] 0 0 0 0 0 0 0 0 0 1 ...
..- attr(*, "dimnames")=List of 3
.. ..$ : chr [1:9] "0" "1" "2" "3" ...
.. ..$ : chr [1:9] "0" "1" "2" "3" ...
.. ..$ : chr [1:536] "0.0329688509639716" "0.0555592940852114" "0.0593206943292609" "0.066534579
$ delta.na   : num [1:9, 1:9, 1:536] -0.00329 0 0 0 0 ...
$ ind.n.risk : num 5
- attr(*, "class")= chr "etm"

> ### Computation of the clfs + var clfs
> clfs <- dli.etm$est["0", "0", ] +
+       dli.etm$est["0", "6", ]
> var.clfs <- dli.etm$cov["0 0", "0 0", ] +
+           dli.etm$cov["0 6", "0 6", ] +
+           2 * dli.etm$cov["0 0", "0 6", ]
> ## computation of the 95% CIs + plot
> ciplus <- clfs + qnorm(0.975) * sqrt(var.clfs)
> cimoins <- clfs - qnorm(0.975) * sqrt(var.clfs)
> plot(dli.etm$time, clfs, type = "s", lwd=3,
+      bty = "n", ylim = c(0, 1), yaxs="i", las=1,
+      xlab = "Time since 1st remission (years)",
+      ylab = "P(CLFS)" )
> lines(dli.etm$time, cimoins, lty = 3, type = "s")
> lines(dli.etm$time, ciplus, lty = 3, type = "s")
> matlines( pr.pt, t(CLFS), lty=c(1,3,3), lwd=c(3,1,1), col="red" )

```

From figure 9 it is pretty clear that the non-parametric approach gives qualitatively the same result as the parametric approach, but also that the non-parametric modelling essentially represents an over-modelling of the shape of the probability of CLFS which is not biologically credible and hence in general should be avoided.

4.1 Linking the Epi and etm packages.

For the sake of completeness we have included a function in `Epi` that automatically converts a `Lexis` object to a data frame of the relevant structure for input into the `etm` package. Note that even though there is an `etm` method for `Lexis` objects, we must call `etm.Lexis` explicitly, because we loaded the `etm` package *after* the `Epi` package, and thus `Epi:::etm` will be masked by `etm:::etm`. Instead we could call `Epi:::etm` explicitly, but that would be really goofy.

```

> xdli.etm <- etm.Lexis( dli )
> str( xdli.etm )
List of 12
 $ est      : num [1:9, 1:9, 1:540] 0.997 0 0 0 0 ...
..- attr(*, "dimnames")=List of 3
.. ..$ : chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
.. ..$ : chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
.. ..$ : chr [1:540] "0.0329688509639716" "0.0555592940852114" "0.0593206943292609" "0.066534579
 $ cov      : num [1:81, 1:81, 1:540] 1.08e-05 0.00 0.00 0.00 0.00 ...
..- attr(*, "dimnames")=List of 3
.. ..$ : chr [1:81, 1] "Rem Rem" "D/Rem Rem" "Rel Rem" "D/Rel Rem" ...
.. ..$ : chr [1:81, 1] "Rem Rem" "D/Rem Rem" "Rel Rem" "D/Rel Rem" ...
.. ..$ : chr [1:540] "0.0329688509639716" "0.0555592940852114" "0.0593206943292609" "0.066534579
 $ time     : num [1:540] 0.033 0.0556 0.0593 0.0665 0.0667 ...
 $ s       : num 0
 $ t       : num 21.1

```

```

$ trans      : 'data.frame':      8 obs. of  2 variables:
..$ from: Factor w/ 4 levels "DLI","Rel","Rem",...: 3 3 2 2 1 1 4 4
..$ to      : Factor w/ 8 levels "D/DLI","D/Rel",...: 3 6 2 5 1 8 4 7
$ state.names: chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
$ cens.name  : chr "cens"
$ n.risk     : int [1:540, 1:4] 304 303 302 301 300 299 298 297 296 295 ...
..- attr(*, "dimnames")=List of 2
.. ..$ : NULL
.. ..$ : chr [1:4] "Rem" "Rel" "DLI" "Rem2"
$ n.event    : int [1:9, 1:9, 1:540] 0 0 0 0 0 0 0 0 1 ...
..- attr(*, "dimnames")=List of 3
.. ..$ : chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
.. ..$ : chr [1:9] "Rem" "D/Rem" "Rel" "D/Rel" ...
.. ..$ : chr [1:540] "0.0329688509639716" "0.0555592940852114" "0.0593206943292609" "0.066534579
$ delta.na   : num [1:9, 1:9, 1:540] -0.00329 0 0 0 0 ...
$ ind.n.risk : num 5
- attr(*, "class")= chr "etm"

> plot( xdli.etm, col=rainbow(15), lty=1, lwd=3,
+       legend.pos="topright", bty="n", yaxs="i" )

```

The resulting graph is shown in figure 10

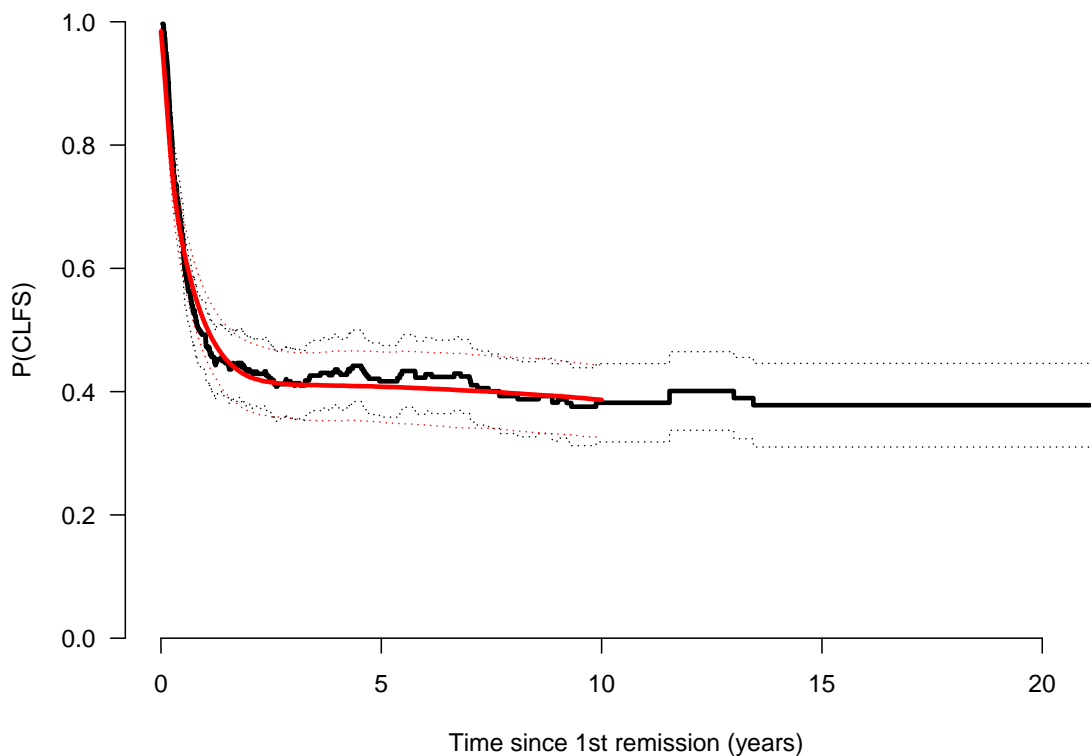


Figure 9: *Estimated CLFS, with confidence bands based on simulation from an assumed normal distribution of the estimates (red curve), compared with the non-parametric curve for the etm package.*

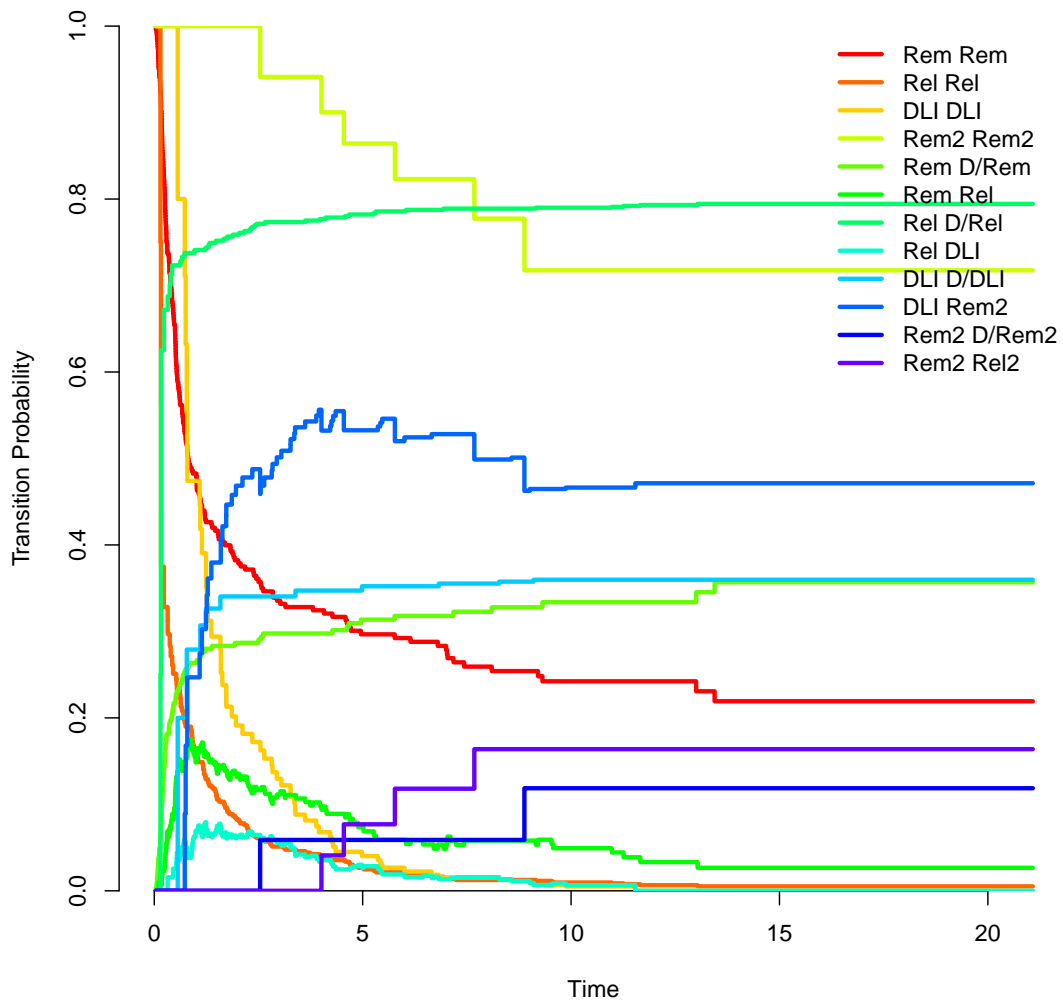


Figure 10: *Estimated transition probabilities between states using the `etm.Lexis` function.*

References

- [1] Arthur Allignol, Martin Schumacher, and Jan Beyersmann. Empirical transition matrix of multi-state models: The etm package. *Journal of Statistical Software*, 38(4):1–15, 1 2011.
- [2] Bendix Carstensen and Martyn Plummer. Using Lexis objects for multi-state models in R. *Journal of Statistical Software*, 38(6):1–18, 1 2011.
- [3] Martyn Plummer and Bendix Carstensen. Lexis: An R class for epidemiological studies with long-term follow-up. *Journal of Statistical Software*, 38(5):1–12, 1 2011.