The resurrection of time as a continuous concept in biostatistics, demography and epidemiology

Bendix Carstensen Steno Diabetes Center,
Gentofte, Denmark
& Department of Biostatistics, University of Copenhagen
`bxc@steno.dk`
`http://BendixCarstensen.com`

IMBEI, Mainz, Germany, 20 September 2016

`http://BendixCarstensen.com/AdvCoh/talks/`

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1. Do not condition on the future
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3. Stick to this world

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- …namely one reached some time in the future
- Normally caused by classification of **persons** instead of classification of **follow-up time**

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- Allows **multiple** timescales, *e.g.* age, duration, calendar time

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…which is indeed **not** of this world.

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- Conceptually t is just a covariate that varies within individual.
- Cox's approach profiles $\lambda_0(t)$ out from the model

The Cox-likelihood as profile likelihood

- One parameter per death time to describe the effect of time (i.e. the chosen timescale).

$$\log\big(\lambda(t, x_i)\big) = \log\big(\lambda_0(t)\big) + \beta_1 x_{1i} + \cdots + \beta_p x_{pi} = \alpha_t + \eta_i$$

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  - Turns out to be Cox's partial likelihood

The Cox-likelihood: mechanics of computing

- The likelihood is computed by suming over risk-sets:

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    - the (only) empirical rate $(1,1)$ with the death at time t.
    - all other empirical rates $(0,1)$ from those who were at risk at time t.

Note: There is one contribution from each person at risk to this part of the log-likelihood:

$$\begin{aligned}
\ell_t(\alpha_t, \beta) &= \sum_{i \in \mathcal{R}_t} d_i \log(\lambda_i(t)) - \lambda_i(t) y_i \\
&= \sum_{i \in \mathcal{R}_t} \left\{ d_i(\alpha_t + \eta_i) - \mathrm{e}^{\alpha_t + \eta_i} \right\} \\
&= \alpha_t + \eta_{\textsf{death}} - \mathrm{e}^{\alpha_t} \sum_{i \in \mathcal{R}_t} \mathrm{e}^{\eta_i}
\end{aligned}$$

where $\eta_{\textsf{death}}$ is the linear predictor for the person that died.

The derivative w.r.t. α_t is:

$$\mathrm{D}_{\alpha_t}\ell_t(\alpha_t,\beta) = 1 - \mathrm{e}^{\alpha_t}\sum_{i\in\mathcal{R}_t}\mathrm{e}^{\eta_i} = 0 \quad\Leftrightarrow\quad \mathrm{e}^{\alpha_t} = \frac{1}{\sum_{i\in\mathcal{R}_t}\mathrm{e}^{\eta_i}}$$

If this estimate is fed back into the log-likelihood for α_t, we get the **profile likelihood** (with α_t "profiled out"):

$$\log\left(\frac{1}{\sum_{i\in\mathcal{R}_t}\mathrm{e}^{\eta_i}}\right) + \eta_{\textsf{death}} - 1 = \log\left(\frac{\mathrm{e}^{\eta_{\textsf{death}}}}{\sum_{i\in\mathcal{R}_t}\mathrm{e}^{\eta_i}}\right) - 1$$

which is the same as the contribution from time t to Cox's partial likelihood.

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- Modelling is by standard `glm` Poisson

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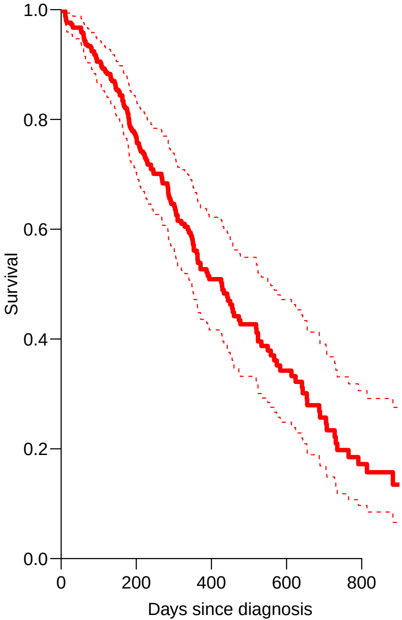
Mayo Clinic lung cancer 60 year old woman



Example: Mayo Clinic lung cancer I

```
> library( survival )
> library( Epi )
> Lung <- Lexis( exit = list( tfe=time ),
+                exit.status = factor(status,labels=c("Alive","Dead")),
+                data = lung )

NOTE: entry.status has been set to "Alive" for all.
NOTE: entry is assumed to be 0 on the tfe timescale.
```

Example: Mayo Clinic lung cancer II

```
> mL.cox <- coxph( Surv( tfe, tfe+lex.dur, lex.Xst=="Dead" ) ~
+                  age + factor( sex ),
+                  method="breslow", eps=10^-8, iter.max=25, data=Lung )
> Lung.s <- splitLexis( Lung,
+                       breaks=c(0,sort(unique(Lung$time))),
+                       time.scale="tfe" )
> Lung.S <- splitLexis( Lung,
+                       breaks=c(0,sort(unique(Lung$time[Lung$lex.Xst=="Dead"])))
+                       time.scale="tfe" )
> summary( Lung.s )

Transitions:
     To
From    Alive Dead  Records:  Events: Risk time:  Persons:
  Alive 19857  165     20022      165      69593       228

> summary( Lung.S )
```

Example: Mayo Clinic lung cancer III

```
Transitions:
     To
From    Alive Dead  Records:  Events: Risk time:  Persons:
  Alive 15916  165     16081      165      69593       228

> subset( Lung.s, lex.id==96 )[,1:11]

     lex.id tfe lex.dur lex.Cst lex.Xst inst time status age sex ph.ecog
9235     96   0       5   Alive   Alive   12   30      2  72   1       2
9236     96   5       6   Alive   Alive   12   30      2  72   1       2
9237     96  11       1   Alive   Alive   12   30      2  72   1       2
9238     96  12       1   Alive   Alive   12   30      2  72   1       2
9239     96  13       2   Alive   Alive   12   30      2  72   1       2
9240     96  15      11   Alive   Alive   12   30      2  72   1       2
9241     96  26       4   Alive    Dead   12   30      2  72   1       2

> nlevels( factor( Lung.s$tfe ) )

[1] 186
```

Example: Mayo Clinic lung cancer IV

```
> system.time(
+ mLs.pois.fc <- glm( lex.Xst=="Dead" ~ - 1 + factor( tfe ) +
+                               age + factor( sex ),
+                               offset = log(lex.dur),
+                     family=poisson, data=Lung.s, eps=10^-8, maxit=25 )
+              )

   user  system elapsed
 10.828   0.012  10.837

> length( coef(mLs.pois.fc) )

[1] 188

> system.time(
+ mLS.pois.fc <- glm( lex.Xst=="Dead" ~ - 1 + factor( tfe ) +
+                               age + factor( sex ),
+                               offset = log(lex.dur),
+                     family=poisson, data=Lung.S, eps=10^-8, maxit=25 )
+              )
```

Example: Mayo Clinic lung cancer V

```
   user  system elapsed 
  3.258   0.000   3.257 

> length( coef(mLS.pois.fc) )

[1] 142

> t.kn <- c(0,25,100,500,1000)
> dim( Ns(Lung.s$tfe,knots=t.kn) )

[1] 20022     4

> system.time(
+ mLs.pois.sp <- glm( lex.Xst=="Dead" ~ Ns( tfe, knots=t.kn ) +
+                                age + factor( sex ),
+                     offset = log(lex.dur),
+                     family=poisson, data=Lung.s, eps=10^-8, maxit=25 )
+             )
```

Example: Mayo Clinic lung cancer VI

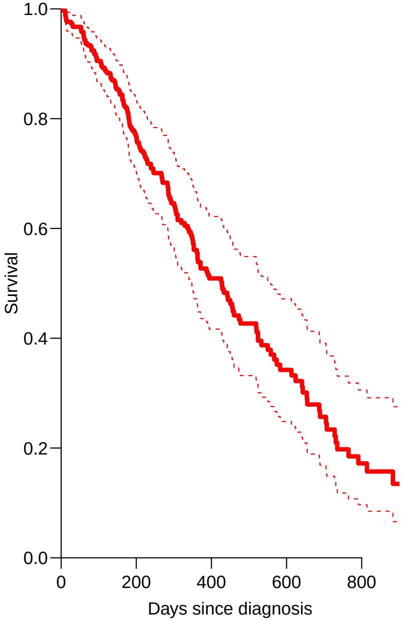
```
   user  system elapsed 
  0.173   0.000   0.172 
```

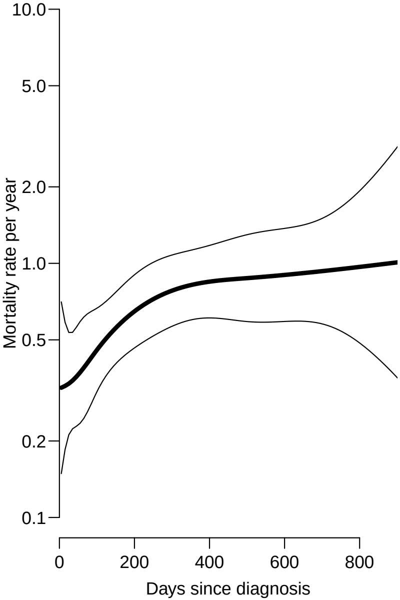
```
> ests <-
+ rbind( ci.exp(mL.cox),
+        ci.exp(mLs.pois.fc,subset=c("age","sex")),
+        ci.exp(mLS.pois.fc,subset=c("age","sex")),
+        ci.exp(mLs.pois.sp,subset=c("age","sex")) )
> cmp <- cbind( ests[c(1,3,5,7)  ,],
+               ests[c(1,3,5,7)+1,] )
> rownames( cmp ) <- c("Cox","Poisson-factor","Poisson-factor (D)","Poisson-spline
> colnames( cmp )[c(1,4)] <- c("age","sex")
```

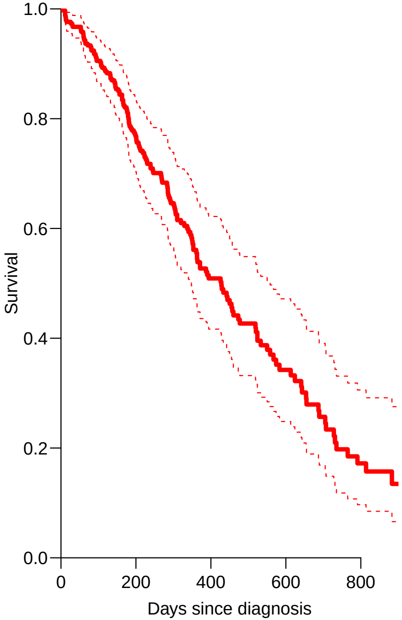
```
> round( cmp, 7 )
```

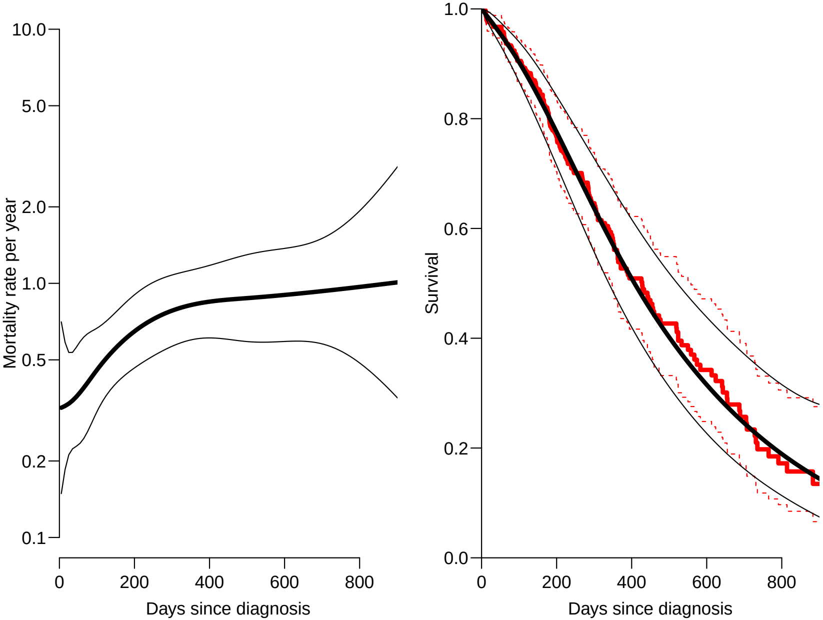
Example: Mayo Clinic lung cancer VII

```
                          age      2.5%    97.5%       sex      2.5%     97.5%
Cox                  1.017158 0.9989388 1.035710 0.5989574 0.4313720 0.8316487
Poisson-factor       1.017158 0.9989388 1.035710 0.5989574 0.4313720 0.8316487
Poisson-factor (D) 1.017332 0.9991211 1.035874 0.5984794 0.4310150 0.8310094
Poisson-spline       1.016189 0.9980329 1.034676 0.5998287 0.4319932 0.8328707
```


1.0
0.8
0.6
0.4
0.2
0.0
Survival
0
200
400
600
800
Days since diagnosis


10.0
5.0
2.0
1.0
0.5
0.2
0.1
Mortality rate per year
0
200
400
600
800
Days since diagnosis


1.0
0.8
0.6
0.4
0.2
0.0
Survival
0
200
400
600
800
Days since diagnosis


10.0
5.0
2.0
1.0
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Mortality rate per year
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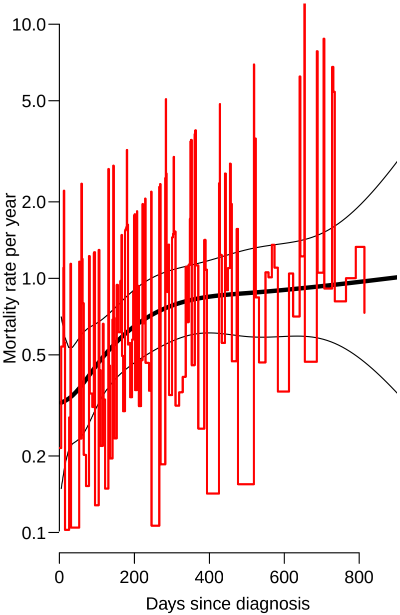
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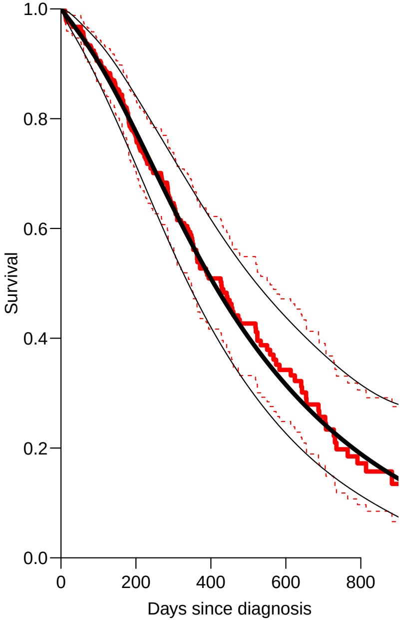
1.0
0.8
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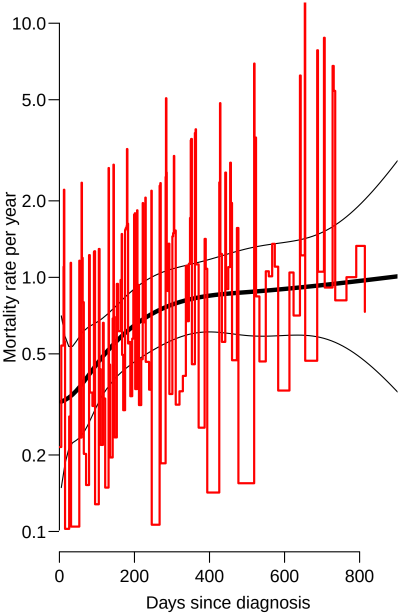
0.4
0.2
0.0
Survival
0
200
400
600
800
Days since diagnosis


10.0
5.0
2.0
1.0
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Mortality rate per year
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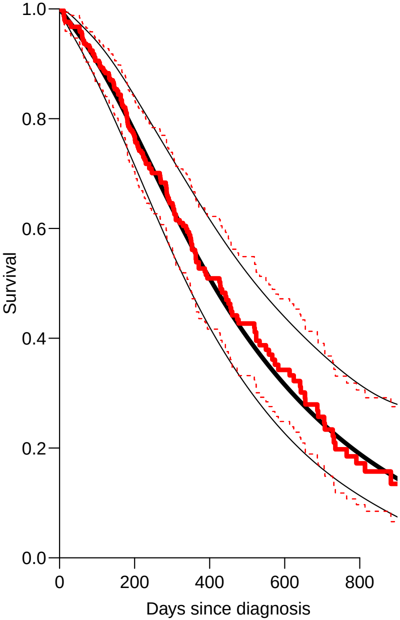
Days since diagnosis


1.0
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0.6
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Survival
0
200
400
600
800
Days since diagnosis

Deriving the survival function

```
> mLs.pois.sp <- glm( lex.Xst=="Dead" ~ Ns( tfe, knots=t.kn ) +
+                               age + factor( sex ),
+                     offset = log(lex.dur),
+                     family=poisson, data=Lung.s, eps=10^-8, maxit=25 )
```

```
> CM <- cbind( 1, Ns( seq(10,1000,10)-5, knots=t.kn ), 60, 1 )
> lambda <- ci.exp( mLs.pois.sp, ctr.mat=CM )
> Lambda <- ci.cum( mLs.pois.sp, ctr.mat=CM, intl=10 )[,-4]
> survP  <- exp(-rbind(0,Lambda))
```

Code and output avaialble in
`http://bendixcarstensen.com/AdvCoh/WNtCMa/`

What the Cox-model really is

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- the **model** for the time scale is really with exchangeable time-intervals.
- $\Rightarrow$ difficult to access the baseline hazard.
- $\Rightarrow$ uninitiated tempted to show survival curves where irrelevant

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Follow-up on several timescales

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- Covariates in analysis of rates:
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  - other (fixed) measurements

Follow-up data in `Epi` — `Lexis` objects

A follow-up study:

```
> round( th, 2 )
    id sex birthdat contrast injecdat volume exitdat exitstat
1    1   2  1916.61        1  1938.79     22 1976.79        1
2  640   2  1896.23        1  1945.77     20 1964.37        1
3 3425   1  1886.97        2  1955.18      0 1956.59        1
4 4017   2  1936.81        2  1957.61      0 1992.14        2
...
```

Timescales of interest:

- Age
- Calendar time
- Time since injection

Definition of `Lexis` object

```
> thL <- Lexis( entry = list( age = injecdat-birthdat,
+                             per = injecdat,
+                             tfi = 0 ),
+                exit = list( per = exitdat ),
+         exit.status = as.numeric(exitstat==1),
+                data = th )
```

:

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`entry` is defined on **three** timescales,

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`entry` is defined on **three** timescales,
but `exit` is only defined on **one** timescale:
Follow-up time is the same on all timescales:

`exitdat - injecdat`

The looks of a `Lexis` object

```
> thL[,1:9]
    age     per tfi lex.dur lex.Cst lex.Xst lex.id
1 22.18 1938.79   0   37.99       0       1      1
2 49.54 1945.77   0   18.59       0       1      2
3 68.20 1955.18   0    1.40       0       1      3
4 20.80 1957.61   0   34.52       0       0      4
...

> summary( thL )
Transitions:
     To
From 0  1 Records:  Events: Risk time:  Persons:
   0 3 20       23       20     512.59        23
```

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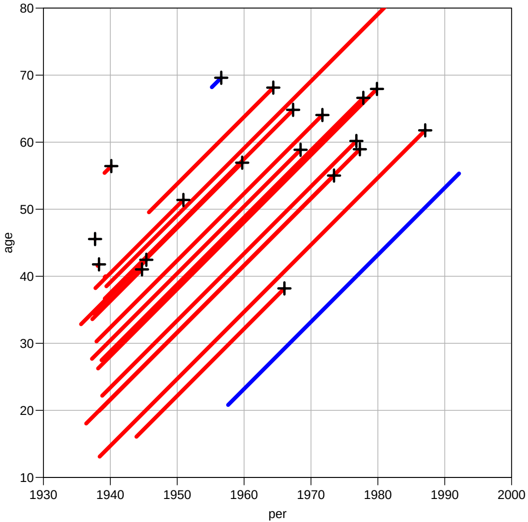

Lexis diagram

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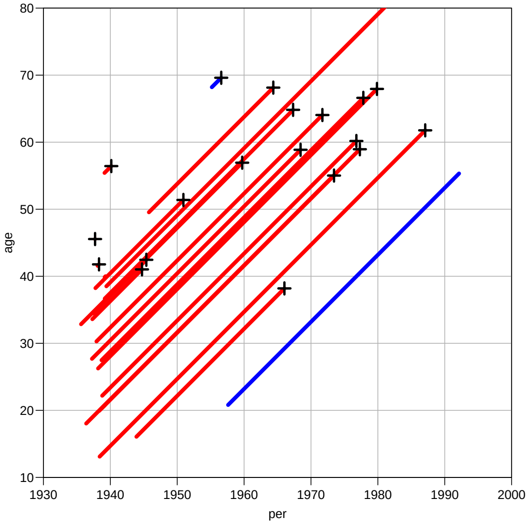

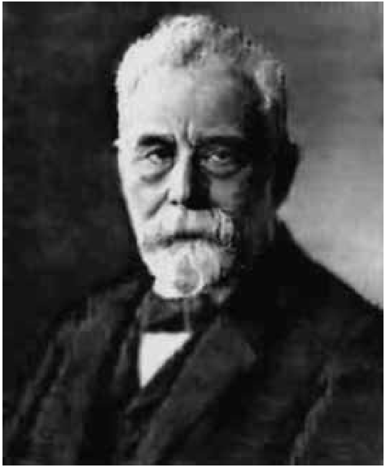

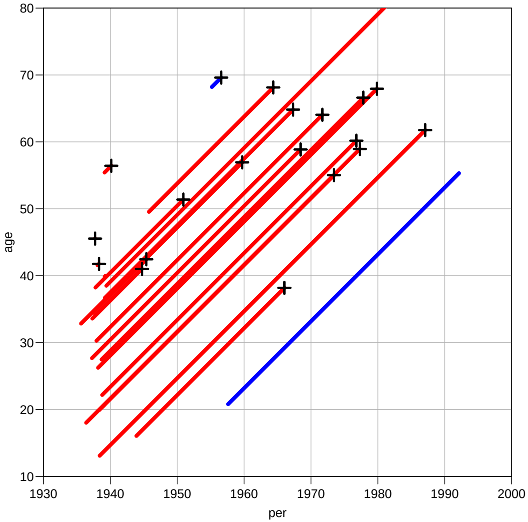

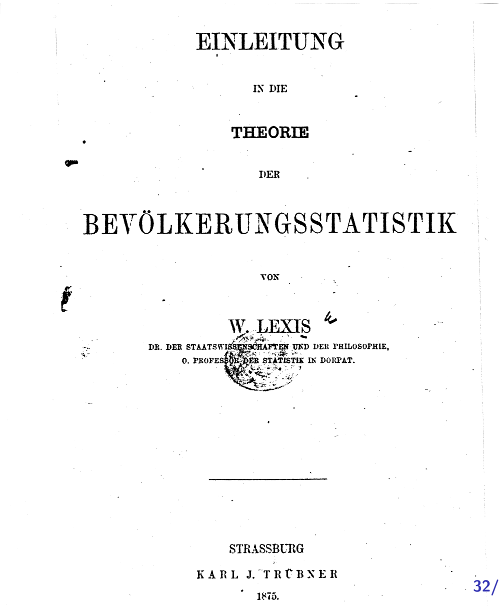

EINLEITUNG

IN DIE

THEORIE

DER

BEVÖLKERUNGSSTATISTIK

VON

W. LEXIS

DR. DER STAATSWISSENSCHAFTEN UND DER PHILOSOPHIE,
O. PROFESSOR DER STATISTIK IN DORPAT.

STRASSBURG
KARL J. TRÜBNER
1875.

Splitting follow-up time

```
> spl1 <- splitLexis( thL, breaks=seq(0,100,20),
>                          time.scale="age" )
> round(spl1,1)
   age    per  tfi lex.dur lex.Cst lex.Xst   id sex birthdat contrast injecdat vo
1 22.2 1938.8  0.0    17.8       0       0    1   2   1916.6        1   1938.8
2 40.0 1956.6 17.8    20.0       0       0    1   2   1916.6        1   1938.8
3 60.0 1976.6 37.8     0.2       0       1    1   2   1916.6        1   1938.8
4 49.5 1945.8  0.0    10.5       0       0  640   2   1896.2        1   1945.8
5 60.0 1956.2 10.5     8.1       0       1  640   2   1896.2        1   1945.8
6 68.2 1955.2  0.0     1.4       0       1 3425   1   1887.0        2   1955.2
7 20.8 1957.6  0.0    19.2       0       0 4017   2   1936.8        2   1957.6
8 40.0 1976.8 19.2    15.3       0       0 4017   2   1936.8        2   1957.6
...
```

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4 49.5 1945.8  0.0    10.5       0       0  640   2   1896.2        1   1945.8
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6 68.2 1955.2  0.0     1.4       0       1 3425   1   1887.0        2   1955.2
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...
```

Splitting follow-up time

```
> spl1 <- splitLexis( thL, breaks=seq(0,100,20),
>                          time.scale="age" )
> round(spl1,1)
   age    per  tfi lex.dur lex.Cst lex.Xst   id sex birthdat contrast injecdat vol
1 22.2 1938.8  0.0    17.8       0       0    1   2   1916.6        1   1938.8
2 40.0 1956.6 17.8    20.0       0       0    1   2   1916.6        1   1938.8
3 60.0 1976.6 37.8     0.2       0       1    1   2   1916.6        1   1938.8
4 49.5 1945.8  0.0    10.5       0       0  640   2   1896.2        1   1945.8
5 60.0 1956.2 10.5     8.1       0       1  640   2   1896.2        1   1945.8
6 68.2 1955.2  0.0     1.4       0       1 3425   1   1887.0        2   1955.2
7 20.8 1957.6  0.0    19.2       0       0 4017   2   1936.8        2   1957.6
8 40.0 1976.8 19.2    15.3       0       0 4017   2   1936.8        2   1957.6
...
```

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   age    per  tfi lex.dur lex.Cst lex.Xst   id sex birthdat contrast injecdat vo
1 22.2 1938.8  0.0    17.8       0       0    1   2   1916.6        1   1938.8
2 40.0 1956.6 17.8    20.0       0       0    1   2   1916.6        1   1938.8
3 60.0 1976.6 37.8     0.2       0       1    1   2   1916.6        1   1938.8
4 49.5 1945.8  0.0    10.5       0       0  640   2   1896.2        1   1945.8
5 60.0 1956.2 10.5     8.1       0       1  640   2   1896.2        1   1945.8
6 68.2 1955.2  0.0     1.4       0       1 3425   1   1887.0        2   1955.2
7 20.8 1957.6  0.0    19.2       0       0 4017   2   1936.8        2   1957.6
8 40.0 1976.8 19.2    15.3       0       0 4017   2   1936.8        2   1957.6
...
```

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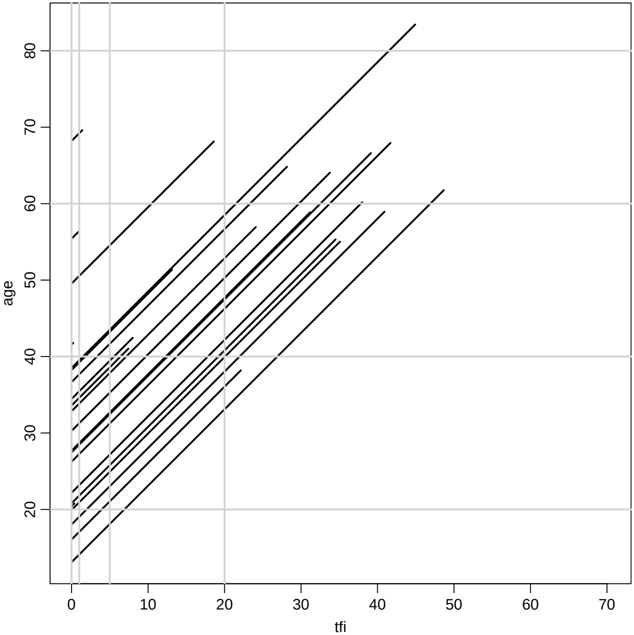
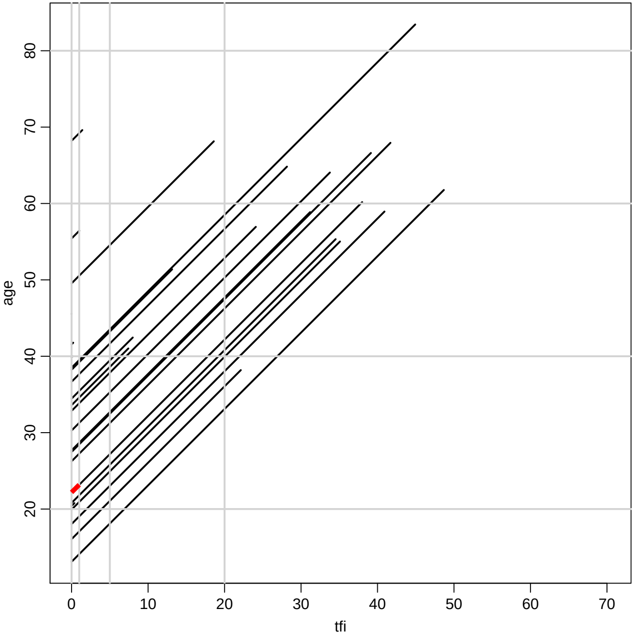
>                          time.scale="age" )
> round(spl1,1)
   age    per  tfi lex.dur lex.Cst lex.Xst   id sex birthdat contrast injecdat vol
1 22.2 1938.8  0.0    17.8       0       0    1   2   1916.6        1   1938.8
2 40.0 1956.6 17.8    20.0       0       0    1   2   1916.6        1   1938.8
3 60.0 1976.6 37.8     0.2       0       1    1   2   1916.6        1   1938.8
4 49.5 1945.8  0.0    10.5       0       0  640   2   1896.2        1   1945.8
5 60.0 1956.2 10.5     8.1       0       1  640   2   1896.2        1   1945.8
6 68.2 1955.2  0.0     1.4       0       1 3425   1   1887.0        2   1955.2
7 20.8 1957.6  0.0    19.2       0       0 4017   2   1936.8        2   1957.6
8 40.0 1976.8 19.2    15.3       0       0 4017   2   1936.8        2   1957.6
...
```

Split on another timescale

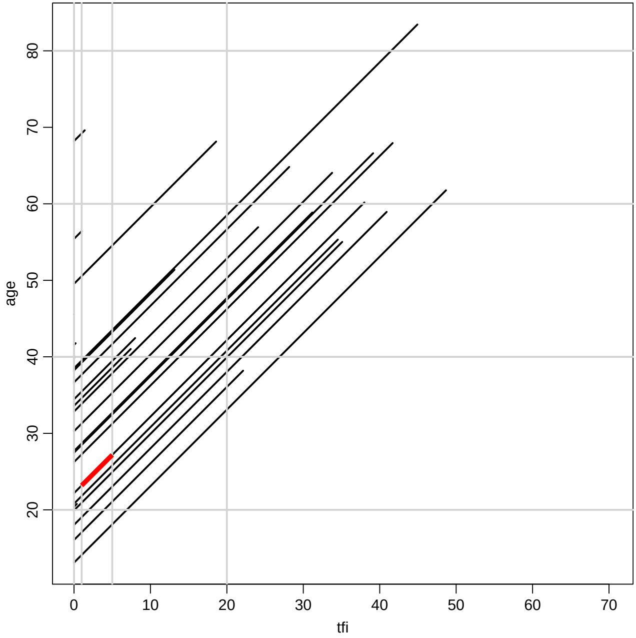
```
> spl2 <- splitLexis( spl1, time.scale="tfi",
                      breaks=c(0,1,5,20,100) )
> round( spl2, 1 )
   lex.id  age    per  tfi lex.dur lex.Cst lex.Xst   id sex birthdat contrast inje
1       1 22.2 1938.8  0.0     1.0       0       0    1   2   1916.6        1   19
2       1 23.2 1939.8  1.0     4.0       0       0    1   2   1916.6        1   19
3       1 27.2 1943.8  5.0    12.8       0       0    1   2   1916.6        1   19
4       1 40.0 1956.6 17.8     2.2       0       0    1   2   1916.6        1   19
5       1 42.2 1958.8 20.0    17.8       0       0    1   2   1916.6        1   19
6       1 60.0 1976.6 37.8     0.2       0       1    1   2   1916.6        1   19
7       2 49.5 1945.8  0.0     1.0       0       0  640   2   1896.2        1   19
8       2 50.5 1946.8  1.0     4.0       0       0  640   2   1896.2        1   19
9       2 54.5 1950.8  5.0     5.5       0       0  640   2   1896.2        1   19
10      2 60.0 1956.2 10.5     8.1       0       1  640   2   1896.2        1   19
11      3 68.2 1955.2  0.0     1.0       0       0 3425   1   1887.0        2   19
12      3 69.2 1956.2  1.0     0.4       0       1 3425   1   1887.0        2   19
13      4 20.8 1957.6  0.0     1.0       0       0 4017   2   1936.8        2   19
14      4 21.8 1958.6  1.0     4.0       0       0 4017   2   1936.8        2   19
15      4 25.8 1962.6  5.0    14.2       0       0 4017   2   1936.8        2   19
16      4 40.0 1976.8 19.2     0.8       0       0 4017   2   1936.8        2   19
17      4 40.8 1977.6 20.0    14.5       0       0 4017   2   1936.8        2   19
```



```
 age  tfi lex.dur lex.Cst lex.Xst
22.2  0.0     1.0       0       0
23.2  1.0     4.0       0       0
27.2  5.0    12.8       0       0
40.0 17.8     2.2       0       0
42.2 20.0    17.8       0       0
60.0 37.8     0.2       0       1
```



```
 age  tfi lex.dur lex.Cst lex.Xst
22.2  0.0     1.0       0       0
23.2  1.0     4.0       0       0
27.2  5.0    12.8       0       0
40.0 17.8     2.2       0       0
42.2 20.0    17.8       0       0
60.0 37.8     0.2       0       1
```



```
 age  tfi lex.dur lex.Cst lex.Xst
22.2  0.0     1.0       0       0
23.2  1.0     4.0       0       0
27.2  5.0    12.8       0       0
40.0 17.8     2.2       0       0
42.2 20.0    17.8       0       0
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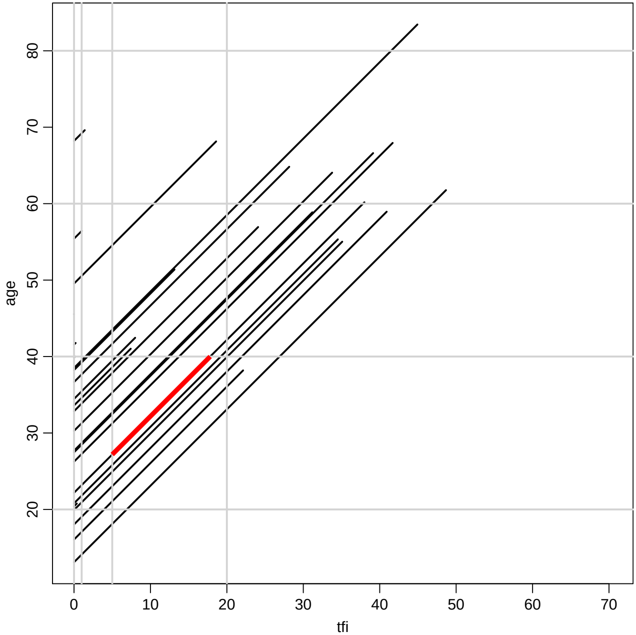

```
 age  tfi lex.dur lex.Cst lex.Xst
22.2  0.0     1.0       0       0
23.2  1.0     4.0       0       0
27.2  5.0    12.8       0       0
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```
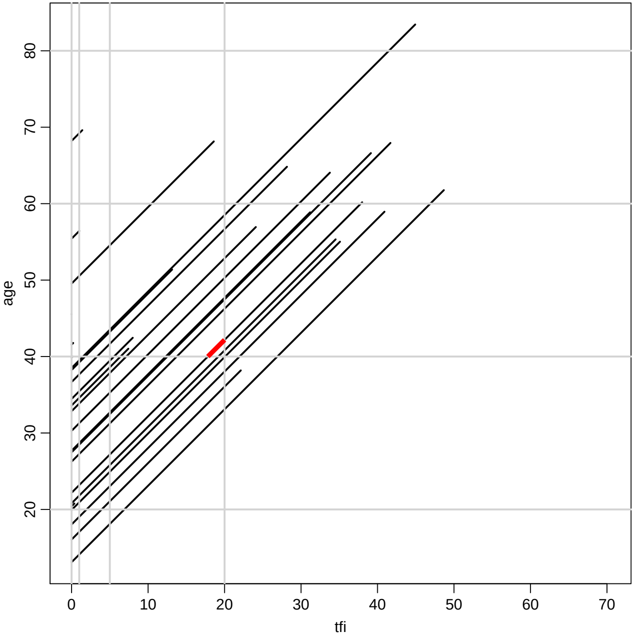
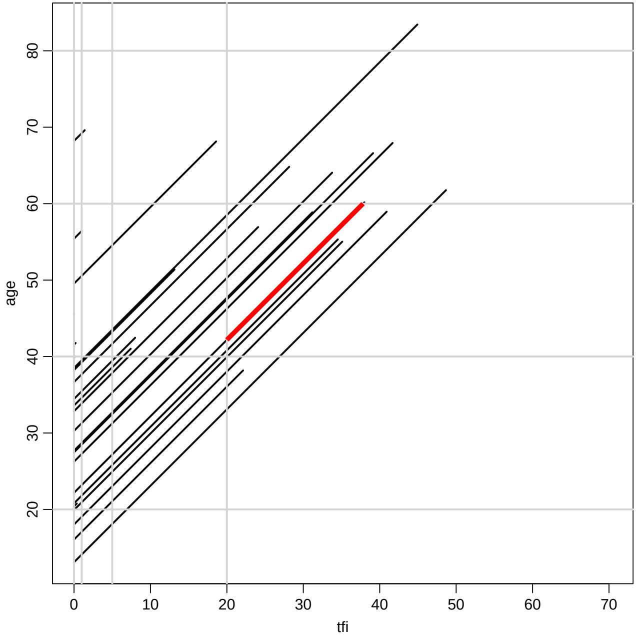
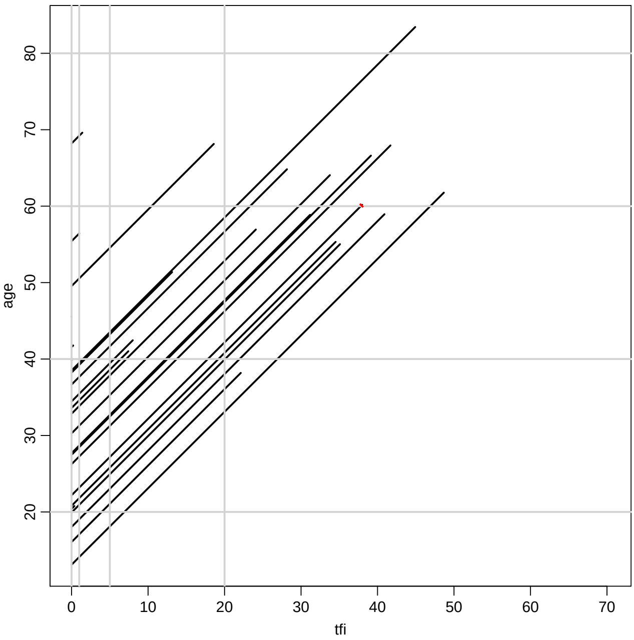



```
 age  tfi lex.dur lex.Cst lex.Xst
22.2  0.0     1.0       0       0
23.2  1.0     4.0       0       0
27.2  5.0    12.8       0       0
40.0 17.8     2.2       0       0
42.2 20.0    17.8       0       0
60.0 37.8     0.2       0       1
```



```
 age  tfi lex.dur lex.Cst lex.Xst
22.2  0.0     1.0       0       0
23.2  1.0     4.0       0       0
27.2  5.0    12.8       0       0
40.0 17.8     2.2       0       0
42.2 20.0    17.8       0       0
60.0 37.8     0.2       0       1
```



```
 age  tfi lex.dur lex.Cst lex.Xst
22.2  0.0     1.0       0       0
23.2  1.0     4.0       0       0
27.2  5.0    12.8       0       0
40.0 17.8     2.2       0       0
42.2 20.0    17.8       0       0
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```

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- And very handy post-processing of results

Markov predictions from non-Markov models

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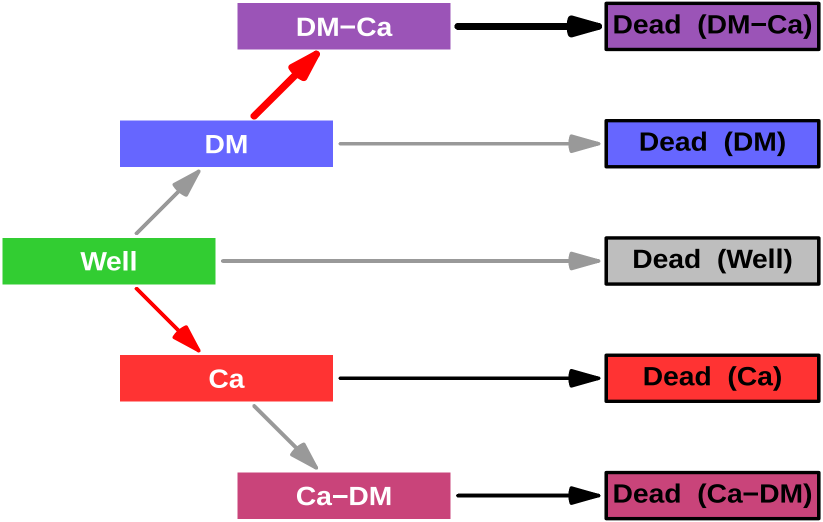
  - . . .
- Easy if rates only depend on age
- — so use cross-sectional rates: $\lambda(a, t = T_0)$

Joint occurrence of Diabetes and Cancer



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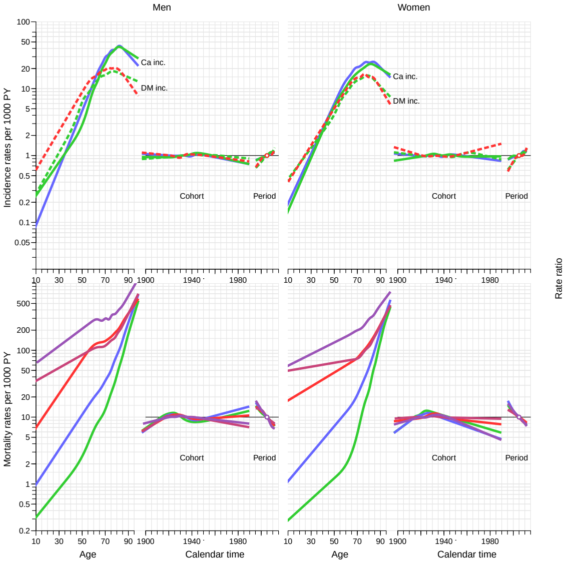
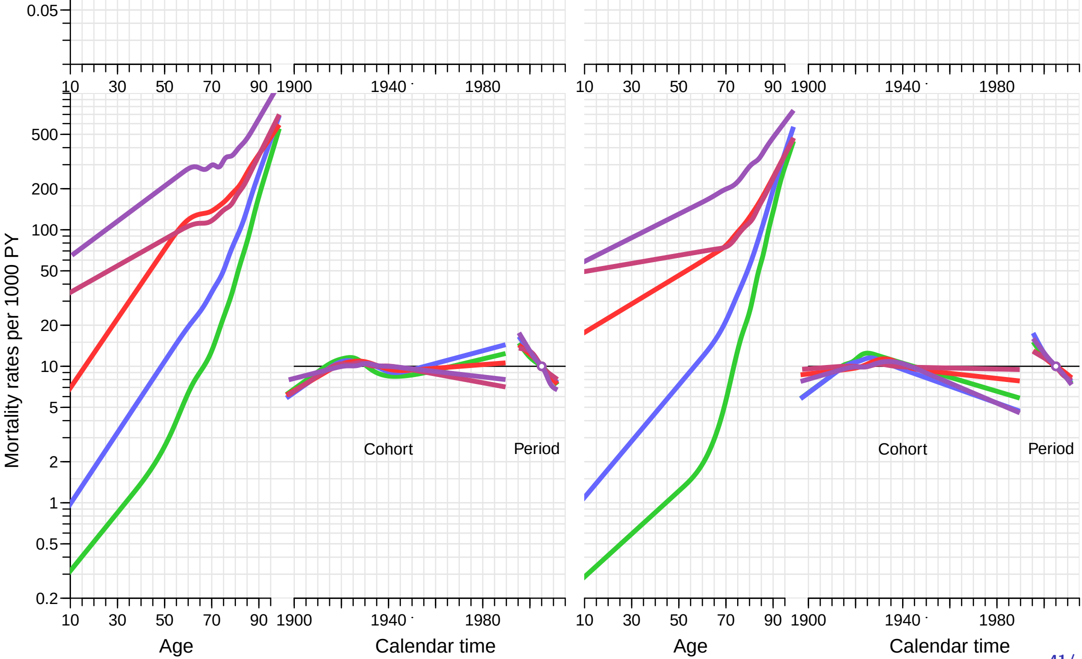
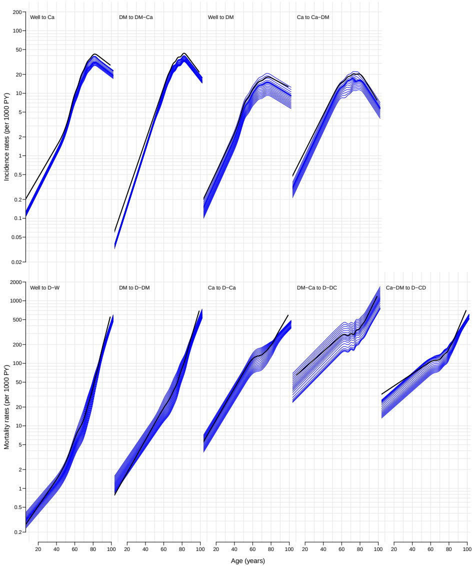
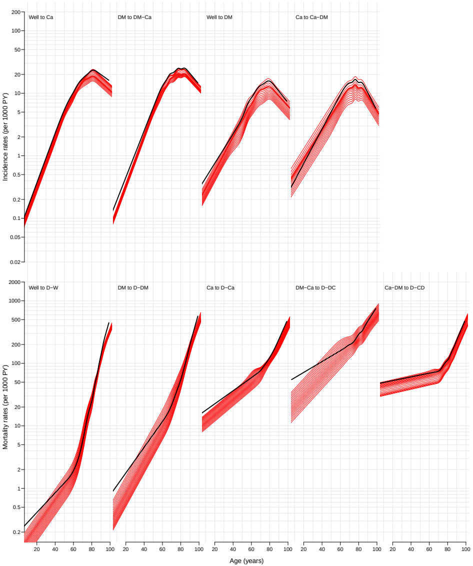



Men
Women
Incidence rates per 1000 PY
100
50
20
10
5
2
1
0.5
0.2
0.1
0.05
Ca inc.
DM inc.
Cohort
Period
10
30
50
70
90
1900
1940
1980
500
200


0.05
10
30
50
70
90
1900
1940
1980
500
200
100
50
20
10
5
2
1
0.5
0.2
Mortality rates per 1000 PY
Cohort
Period
Age
Calendar time

Predicted rates — cross-sectional 1995–2010





Continuous rates (per 2010)

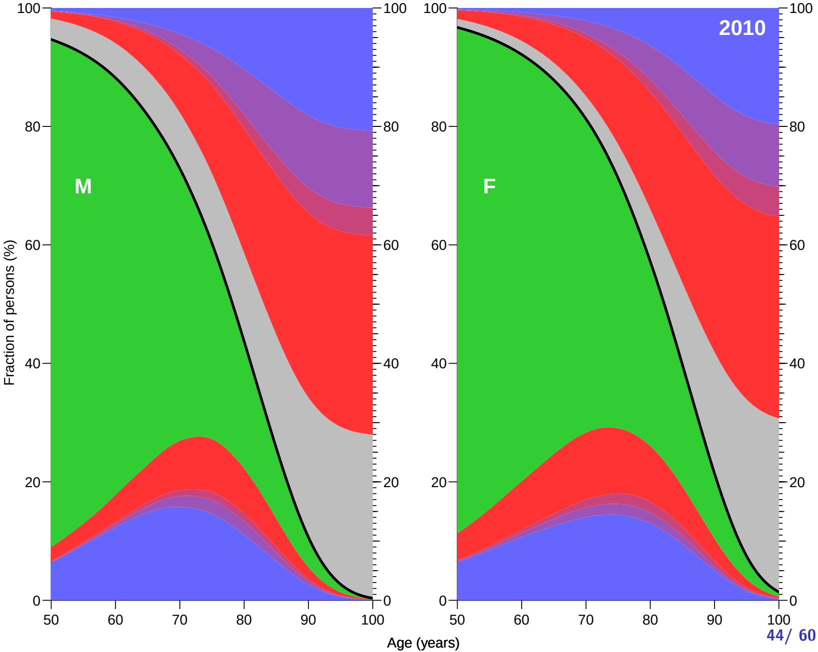
1-month cumulative rates → transition probabilities

$$\Big(1 - \exp\big(-(\Lambda_1 + \Lambda_2 + \Lambda_3)\big)\Big) \times \Lambda_i / (\Lambda_1 + \Lambda_2 + \Lambda_3), i = 1, 2, 3$$

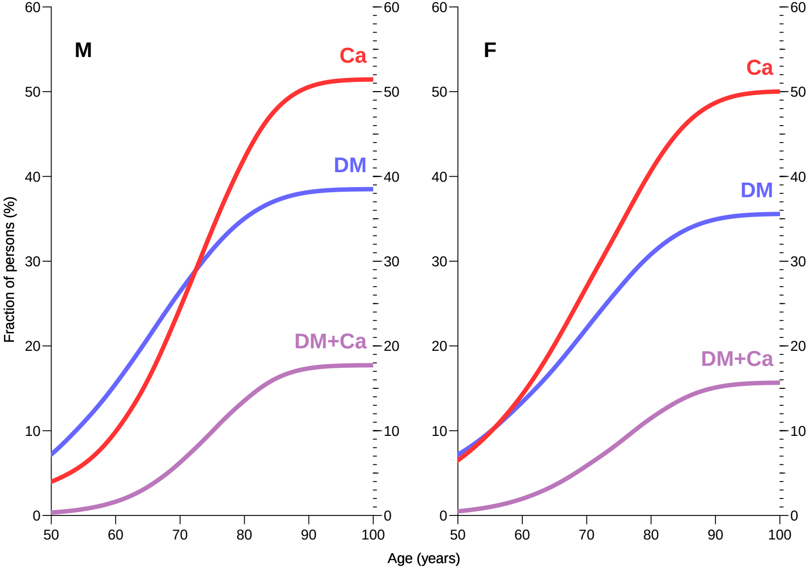
1-month transition probabilities $(\times 10^4)$ at age 66 years:

```
       to
from     Well    DM DM-Ca    Ca Ca-DM   D-W  D-DM  D-Ca  D-DC  D-CD   Sum
  Well   9966     8     .    13     .    14     .     .     .     . 10000
  DM        .  9943    16     .     .     .    41     .     .     . 10000
  DM-Ca     .     .  9582     .     .     .     .     .   418     . 10000
  Ca        .     .     .  9819     9     .     .   172     .     . 10000
  Ca-DM     .     .     .     .  9866     .     .     .     .   134 10000
  D-W       .     .     .     .     . 10000     .     .     .     . 10000
  D-DM      .     .     .     .     .     . 10000     .     .     . 10000
  D-Ca      .     .     .     .     .     .     . 10000     .     . 10000
  D-DC      .     .     .     .     .     .     .     . 10000     . 10000
  D-CD      .     .     .     .     .     .     .     .     . 10000 10000
```

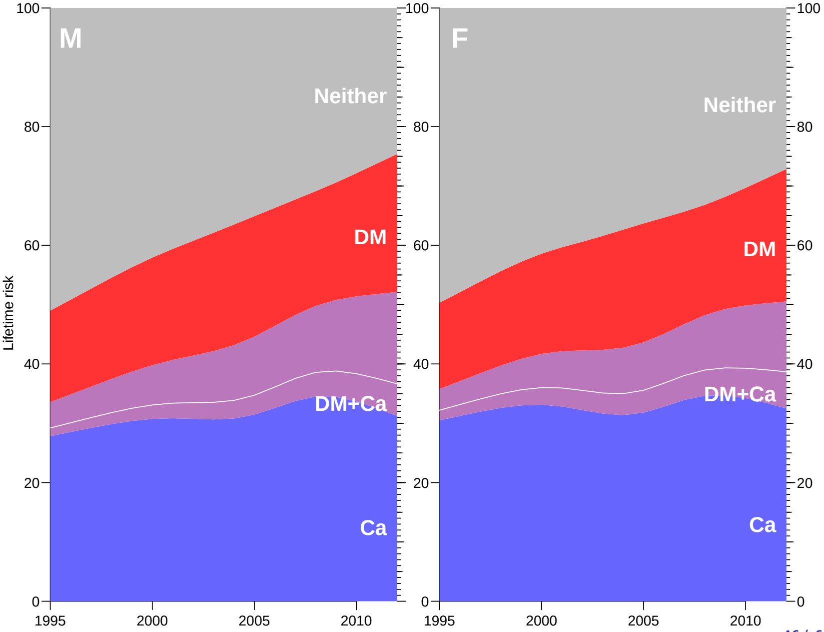
State occupancy probabilities



Lifetime risk



Trend in lifetime risk



Continuous time rates

- Transition rates between states:

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  - based on 1-year tabulation of data

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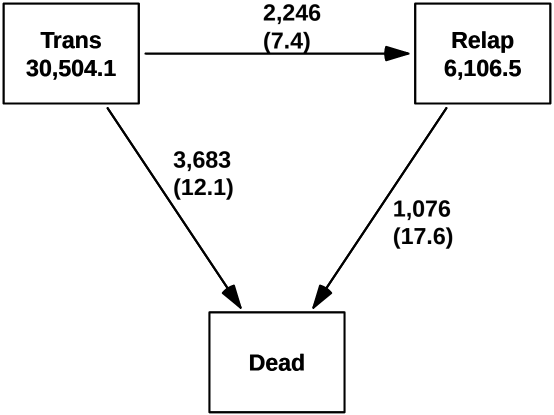
…simplified by a parametric form for rates as function of time

EBMT transplant data

Iacobelli & Carstensen: Multistate Models with Multiple Timescales, Stat Med 2013, [3]



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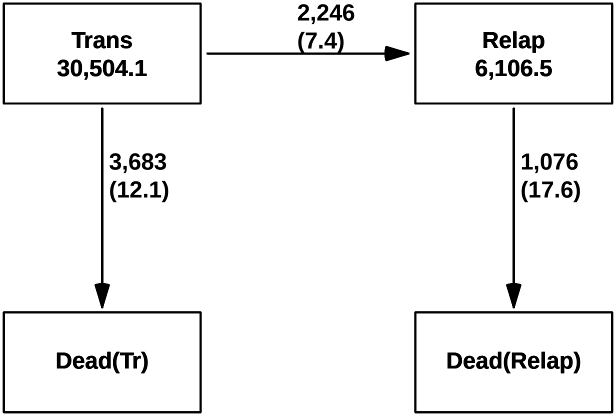

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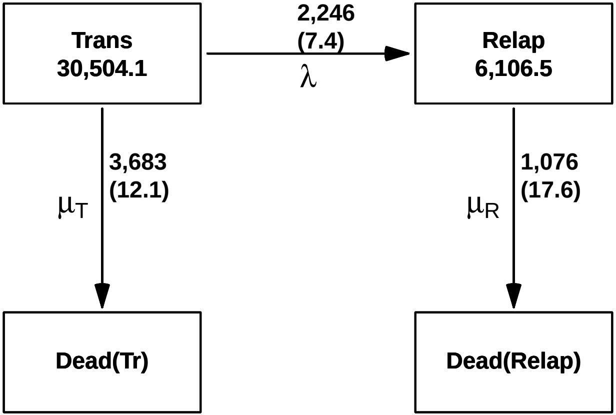

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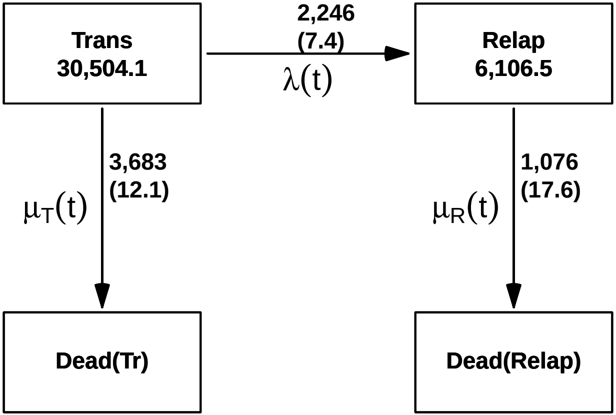

Trans
30,504.1

2,246
(7.4)
$\lambda(t)$

Relap
6,106.5

$\mu_T(t)$
3,683
(12.1)

$\mu_R(t)$
1,076
(17.6)

Dead(Tr)

Dead(Relap)

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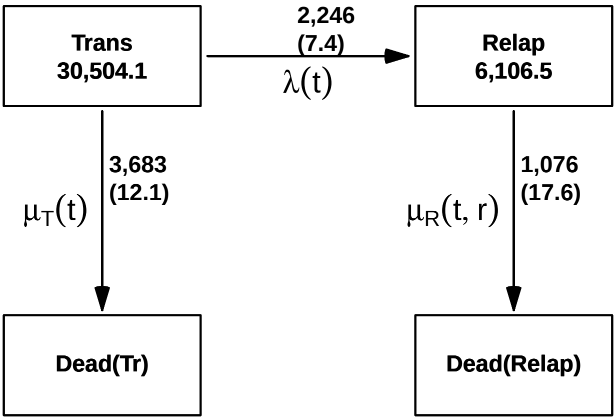

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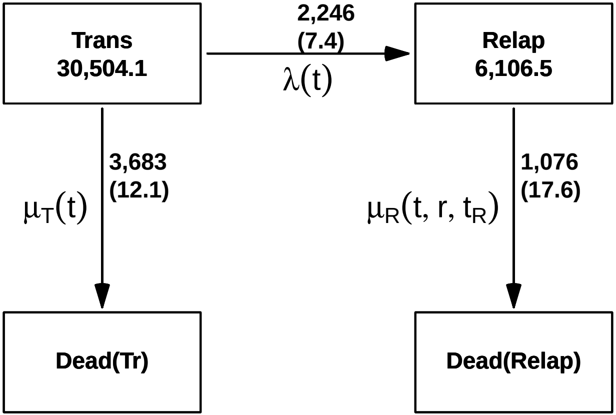

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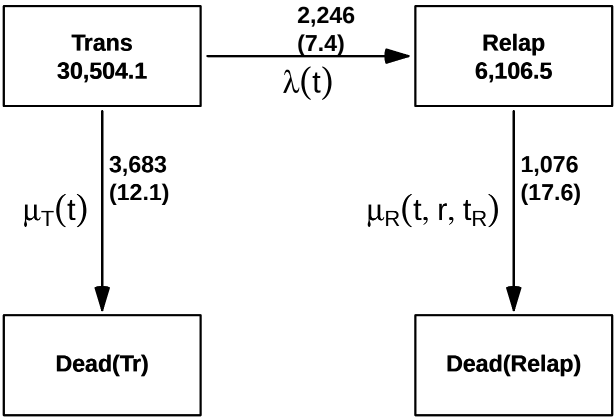

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(12.1)

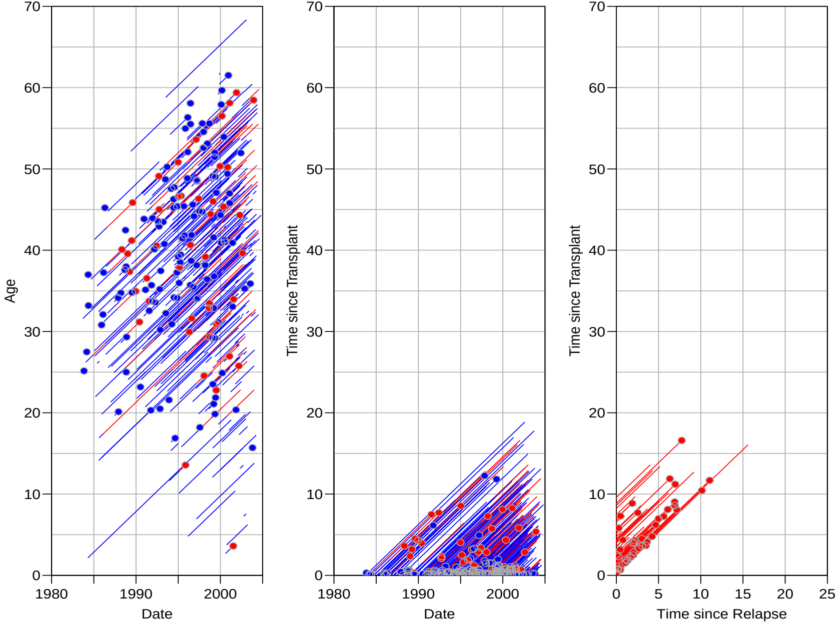
$\mu_R(t, r, t_R)$

1,076
(17.6)

Dead(Tr)

Dead(Relap)

other covariates: Age and date at Tx, sex, donor type, CML type


Age
0
10
20
30
40
50
60
70
1980
1990
2000
Date
Time since Transplant
0
10
20
30
40
50
60
70
1980
1990
2000
Date
Time since Transplant
0
10
20
30
40
50
60
70
0
5
10
15
20
25
Time since Relapse

Markov property: Empirical question

Model for mortality rates:

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- `Lexis` machinery from the **Epi** package for **R**
- …for representation and manipulation of follow-up data.

Using the Lexis machinery [4, 5]

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cmlT <- Lexis(entry = list(cal = cal.yr(dot),
                           age = cal.yr(dot)-cal.yr(dob),
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cmlL <- cutLexis( cmlT, cut = cal.yr(cmlT$dor),
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> subset( cmlL, lex.id==151 )[,1:8]

 id     cal    age  tst  tsr lex.dur lex.Cst lex.Xst  covariates
151 1987.28 36.22 0.00  NA    1.87   Trans   Relap  ...
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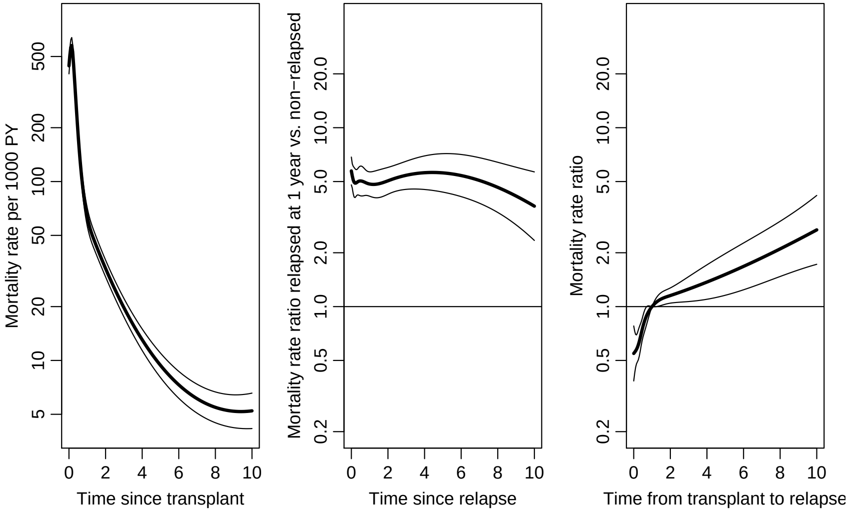
$$\log(\mu) = h(t) + k(r) + g(t - r) + X\beta$$



t: time since transplant r: time since relapse

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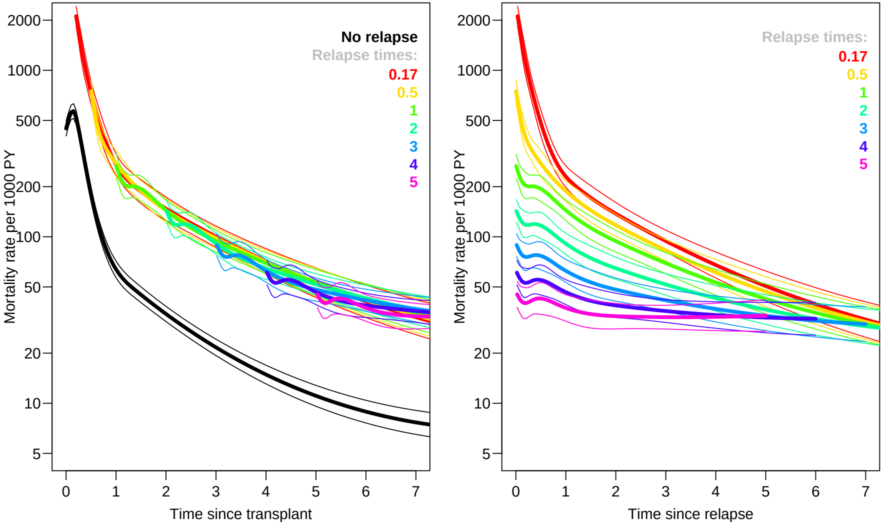

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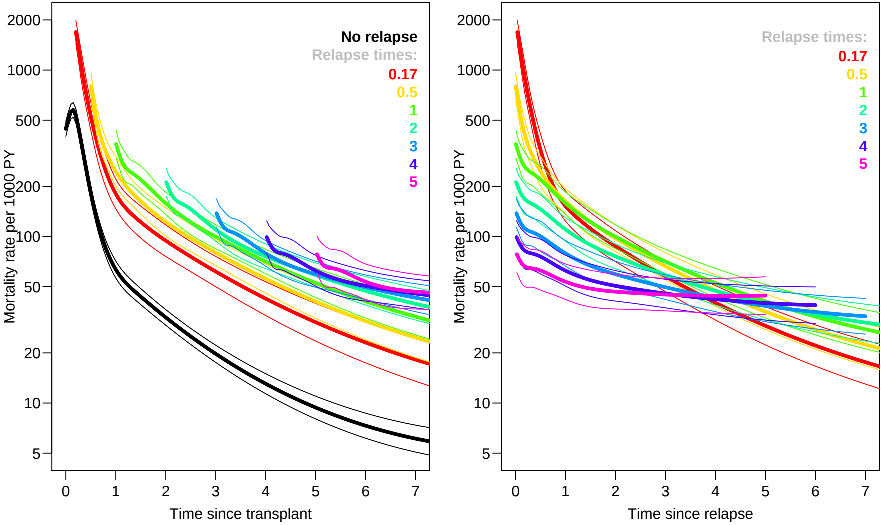
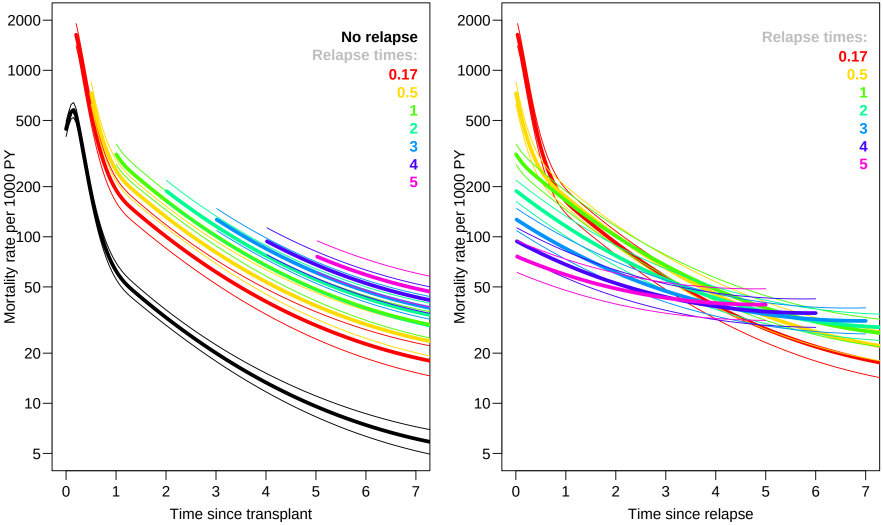


t: time since transplant r: time since relapse

$$\log(\mu) = h(t) \qquad {\color{blue}+g(t-r)} + X\beta$$



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- …unfortunately not a Markov model

Not Markov: the hard way

$$\mathrm{P}\left\{\text{T at } t\right\} = \exp\left(-\int_0^t \lambda(s) + \mu_T(s)\,\mathrm{d}s \right)$$

$$\mathrm{P}\left\{\text{D(T) at } t\right\} = \int_0^t \mu_T(s) \exp\left(-\int_0^s \lambda(u) + \mu_T(u)\,\mathrm{d}u \right) \mathrm{d}s$$

$$\begin{aligned}\mathrm{P}\left\{\text{R at } t\right\} &= \int_0^t \mathrm{P}\left\{\text{Relapsed at } s\right\} \\ &\quad \times \mathrm{P}\left\{\text{Survive in Relapse from } s \text{ to } t\right\} \mathrm{d}s \\ &= \int_0^t \lambda(s) \exp\left(-\int_0^s \lambda(u) + \mu_T(u)\,\mathrm{d}u \right) \\ &\quad \times \exp\left(-\int_s^t \mu_R(u, s)\,\mathrm{d}u \right) \mathrm{d}s\end{aligned}$$

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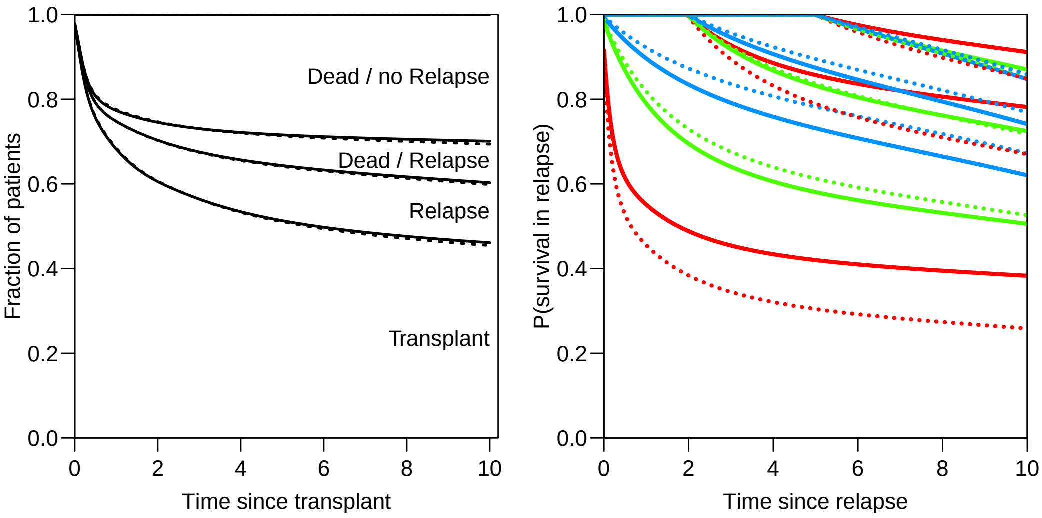

Dotted lines: Markov model, time since transplant
Full lines: $+$ time from Tx to Rel for the μ_R

Rel at: 2 mth, 1 y, 3 y

Summary & Conclusions

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Thanks for your attention

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