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

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Inference in Multistate models

P.K. Andersen & N. Keiding
Interpretability and Importance of Functionals in Competing Risks and Multistate Models, *Stat Med, 2011* [1]:

1. Do not condition on the future
2. Do not regard individuals at risk after they have died
3. Stick to this world

Conditioning on the future

- ...also known as "Immortal time bias", see *e.g.* S. Suissa: Immortal time bias in pharmaco-epidemiology, *Am. J. Epidemiol*, 2008 [2].
- Including persons' follow-up in the wrong state
- ...namely one reached some time in the future
- Normally caused by classification of **persons** instead of classification of **follow-up time**

Why these mistakes?

- Time is usually absent from survival analysis results
- . . . because time is taken to be a **response** variable observed for each **person**
- Unit of analysis is often seen as the person
- Non/Semi-parametric survival model interface invites this misconception
- **Persons** classified by exposure (the latest, often)
- The **real** unit of observation should be person-**time**
- . . . intervals of time, each with different **value** of
  - time
  - other covariates

Time

- Time is a **covariate** — determinant of rates
- **Response** variable in survival / follow-up is bivariate:
  - **Differences** on the timescale (**risk** time, "exposure")
  - **Events**
- The relevant unit of observation is person-time:
  - small intervals of follow-up — "empirical rates"
  - (d_{it}, y_{it}): (event, (sojourn) time) for individual i at time t.
  - y is the **response** time, t is the **covariate** time
- Covariates relate to each interval of follow-up
- Allows **multiple** timescales, *e.g.* age, duration, calendar time

"Stick to this world"

In the paper by Andersen & Keiding this is primarily aimed at the use of "net survival", that is the calculation of

$$\exp\left(-\int_0^t \lambda_c(s)\,\mathrm{d}s\right)$$

for a single cause of death
— formally for a non-exhaustive exit rate from a state.

Survival probability in the situation where:

1. all other causes of death are absent
2. the mortality, λ_c from cause c is unchanged

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

Sticking to this world

- A further feature of “this world”:
- it is **continuous**
- no thresholds in the effect of time
- specifically, death and disease rates vary **smoothly** by
  - age
  - calendar time
  - disease duration
  - ...

A look at the Cox model

$$\lambda(t, x) = \lambda_0(t) \times \exp(x'\beta)$$

A model for the rate as a function of t and x.

The covariate t has a special status:

- Computationally, because all individuals contribute to (some of) the range of t.
- ...the scale along which time is split (the risk sets)
- 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).

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

- Profile likelihood:
  - Derive estimates of α_t as function of data and βs — assuming constant rate between death times
  - Insert in likelihood, now only a function of data and βs
  - Turns out to be Cox's partial likelihood

The Cox-likelihood: mechanics of computing

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

$$\ell(\eta) = \sum_t \log\left(\frac{e^{\eta_{\text{death}}}}{\sum_{i \in \mathcal{R}_t} e^{\eta_i}}\right)$$

- this is essentially splitting follow-up time at event- (and censoring) times
- ...repeatedly in every cycle of the iteration
- ...simplified by not keeping track of risk time
- ...but only works along **one** time scale

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

- Suppose the time scale has been divided into small intervals with at most one death in each:
- Empirical rates: (d_{it}, y_{it}) — each t has at most one $d_{it} = 0$.
- Assume w.l.o.g. the ys in the empirical rates all are 1.
- Log-likelihood contributions that contain information on a specific time-scale parameter α_t will be from:
  - 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"):

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

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

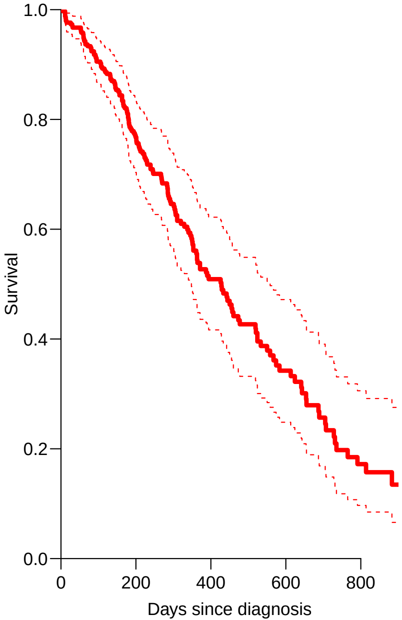
Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — each individual contributes many empirical rates
- (one per risk-set contribution in Cox-modelling)
- From each empirical rate we get:
  - Poisson-response d
  - Risk time $y \to \log(y)$ as offset
  - Covariate value for the timescale
    (time since entry, current age, current date, ...)
  - other covariates
- Contributions not independent, but likelihood is a product
- Same likelihood as for independent Poisson variates
- Modelling is by standard `glm` Poisson

Example: Mayo Clinic lung cancer

- Survival after lung cancer
- Covariates:
  - Age at diagnosis
  - Sex
  - Time since diagnosis
- Cox model
- Split data:
  - Poisson model, time as factor
  - Poisson model, time as spline

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

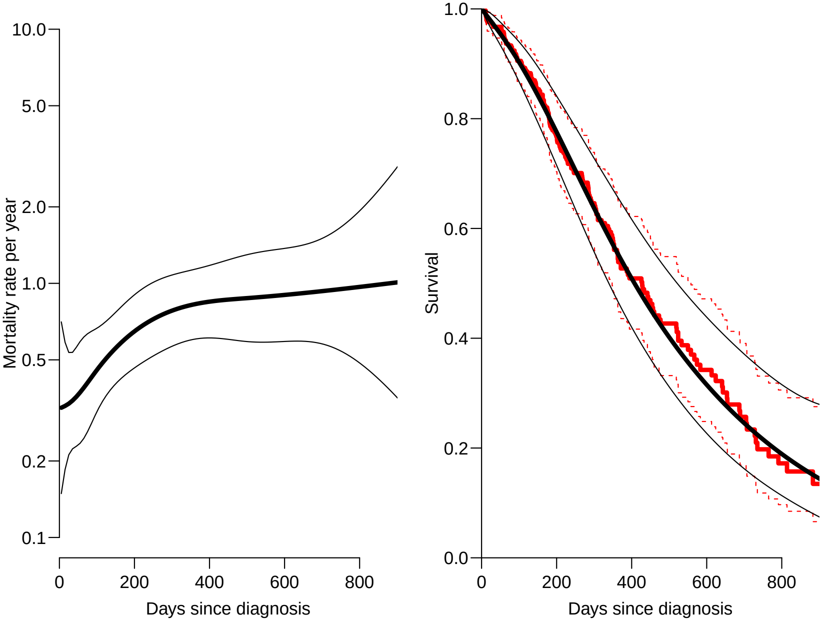
```
   user  system elapsed
  0.173   0.000   0.172
```

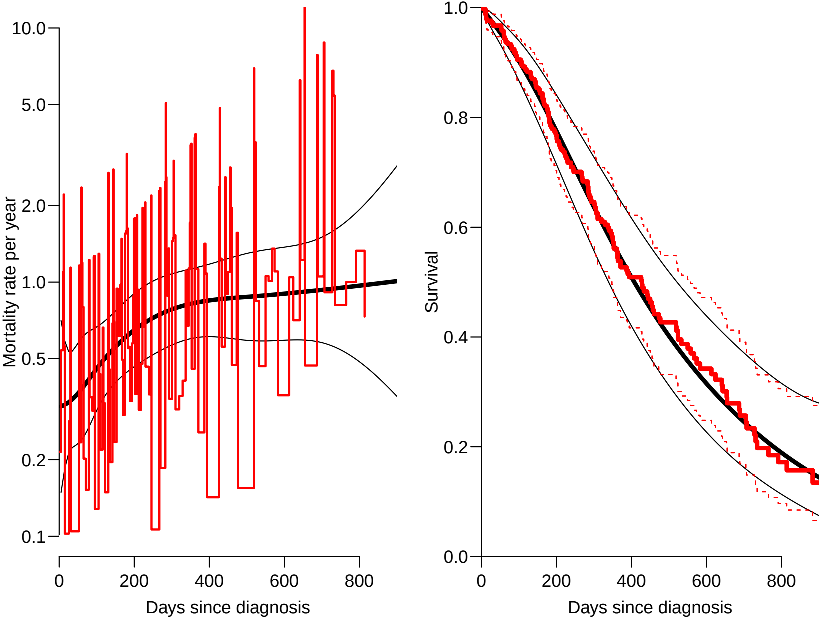
```
> ests <-
+ rbind( ci.exp(mL.cox),
+        ci.exp(mLs.pois.fc,subset=c("age","sex")),
+        ci.exp(mLS.pois.fc,subset=c("age","sex")),
+        ci.exp(mLs.pois.sp,subset=c("age","sex")) )
> cmp <- cbind( ests[c(1,3,5,7)  ,],
+               ests[c(1,3,5,7)+1,] )
> rownames( cmp ) <- c("Cox","Poisson-factor","Poisson-factor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


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



Mortality rate per year
10.0
5.0
2.0
1.0
0.5
0.2
0.1
0
200
400
600
800
Days since diagnosis
Survival
1.0
0.8
0.6
0.4
0.2
0.0
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

Taking the life-table approach *ad absurdum* by:

- dividing time very finely and
- modeling one covariate, the time-scale, with one parameter per distinct value.
- 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

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant
  - Splines (linear, quadratic or cubic)
  - Fractional polynomials
- Brings model into "this world":
  - smoothly varying rates
  - parametric closed form representation of baseline hazard
  - finite no. of parameters
- Makes it really easy to use in calculations of
  - expected residual life time
  - state occupancy probabilities in multistate models
  - ...

Follow-up on several timescales

- The risk-time is the same on all timescales
- Only need the entry point on each time scale:
  - Age at entry.
  - Date of entry.
  - Time since treatment at entry.
    — if time of treatment is the entry, this is 0 for all.
- Response variable in analysis of rates:

$$(d, y) \qquad (\text{event}, \text{duration})$$

- Covariates in analysis of rates:
  - timescales
  - 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 )
```

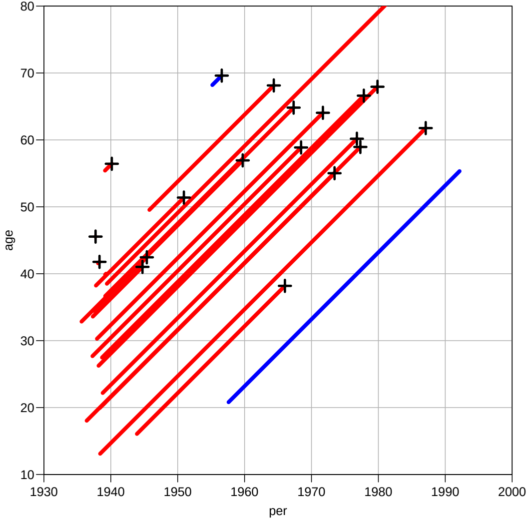
`entry` is defined on **three** timescales,
but `exit` is only defined on **one** timescale:
Follow-up time is the same on all timescales:

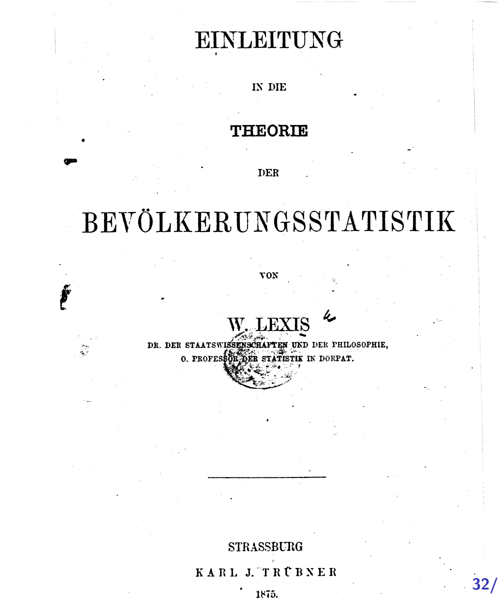
`exitdat - injecdat`

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
```

Lexis diagram




EINLEITUNG

IN DIE

THEORIE

DER

BEVÖLKERUNGSSTATISTIK

VON

W. LEXIS

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

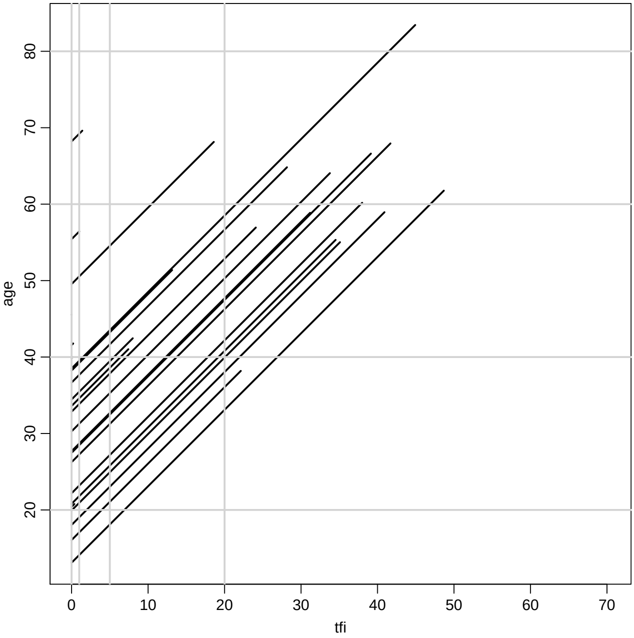
STRASSBURG
KARL J. TRÜBNER
1875.

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 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

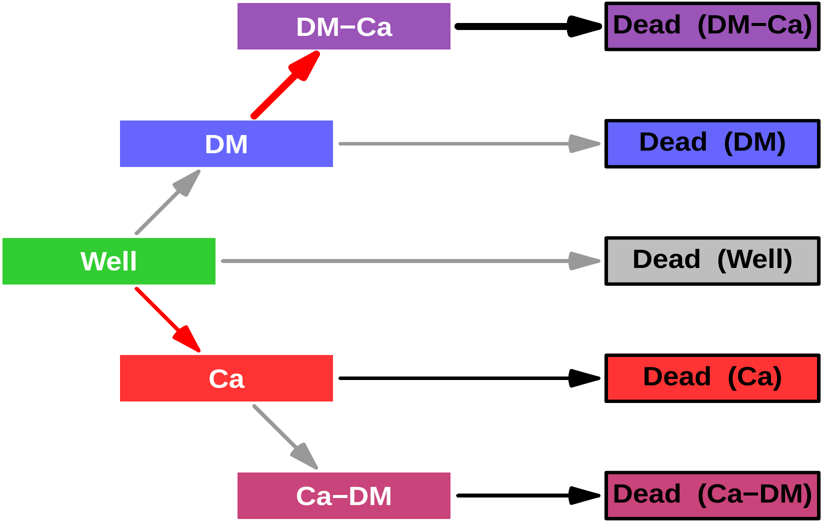
Analysis of results

- d_{it} — events in the variable: `lex.Xst`:
  In the model as response: `lex.Xst==1`
- y_{it} — risk time: `lex.dur` (duration):
  In the model as offset $\log(y)$, `log(lex.dur)`.
- Covariates are:
  - timescales (age, period, time in study)
    — non-linear, continuous effect
  - other variables for this person (constant in each interval).
- If intervals sufficiently small, a very good approximation to a continuously varying rate by using time points from each interval
- And very handy post-processing of results

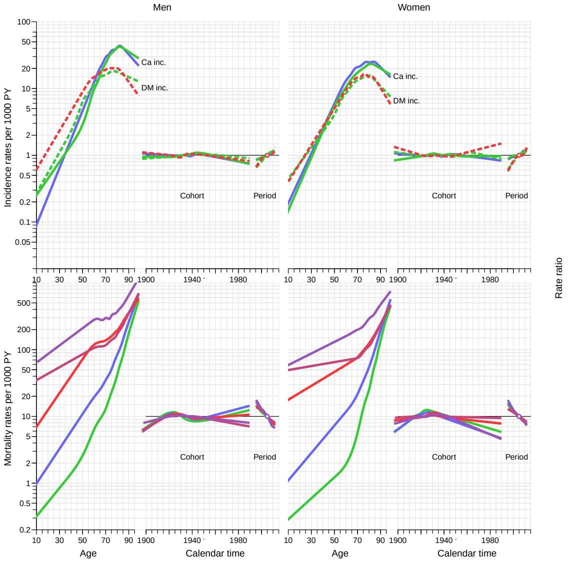
Markov predictions from non-Markov models

- Model rates in a Lexis diagram (age / calendar time): $\lambda(a, t)$
- Aim is summary measures:
  - Expected life time
  - Lifetime probability of disease
  - Lifetime spent diseased
  - ...
- Easy if rates only depend on age
- — so use cross-sectional rates: $\lambda(a, t = T_0)$

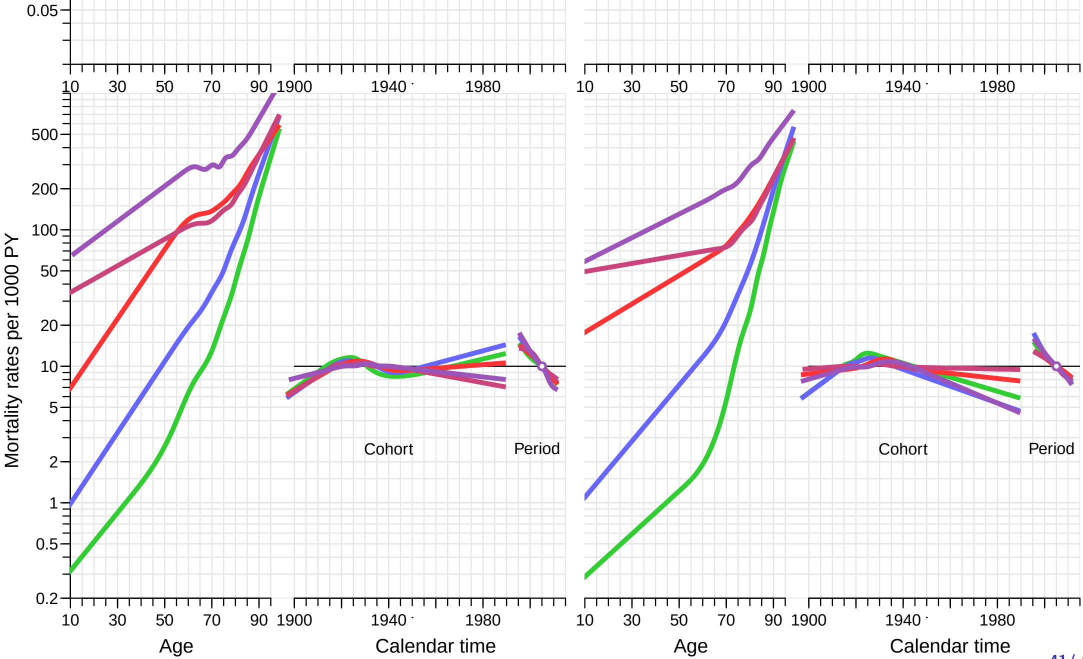
Joint occurrence of Diabetes and Cancer



Joint occurrence of Diabetes and Cancer

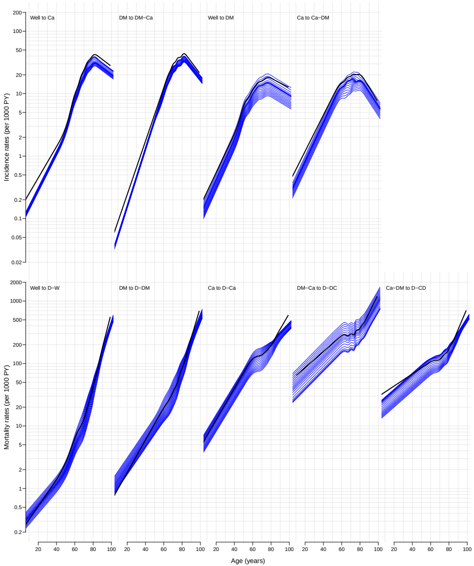


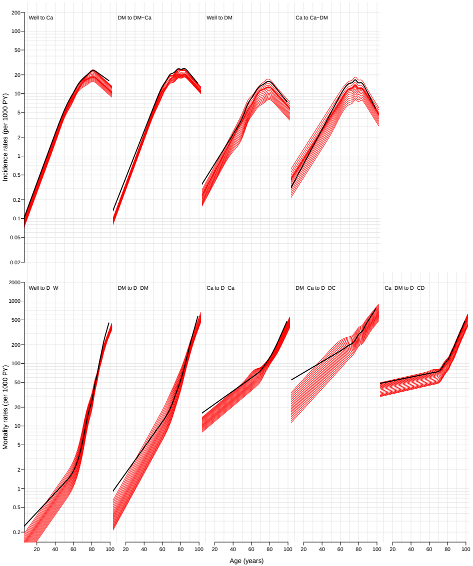
Men
Women
Incidence rates per 1000 PY
100
50
20
10
5
2
1
0.5
0.2
0.1
0.05
Ca inc.
DM inc.
Ca inc.
DM inc.
Cohort
Period
Cohort
Period
10
30
50
70
90
1900
1940
1980
10
30
50
70
90
1900
1940
1980
500
200



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

Predicted rates — cross-sectional 1995–2010





Continuous rates (per 2010)

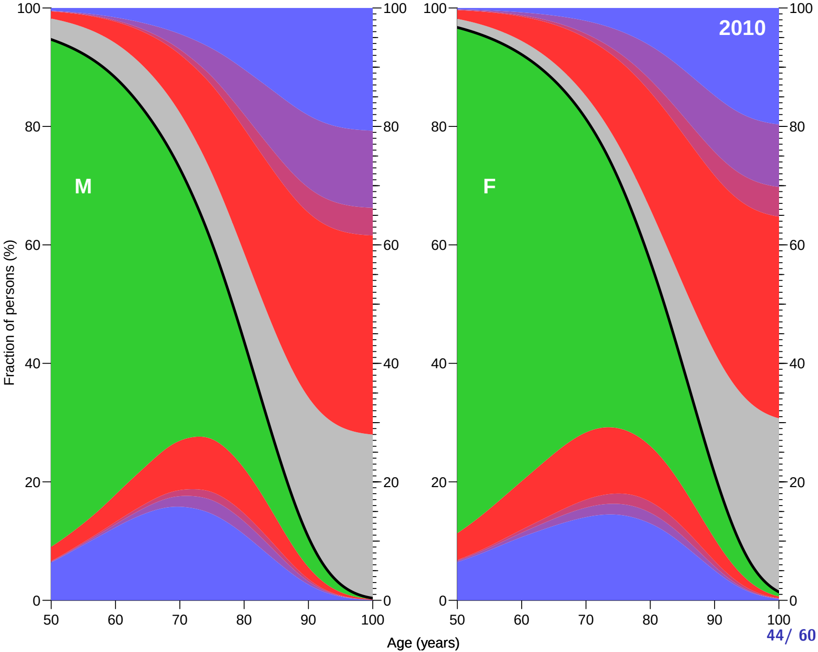
1-month cumulative rates $\rightarrow$ transition probabilities

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

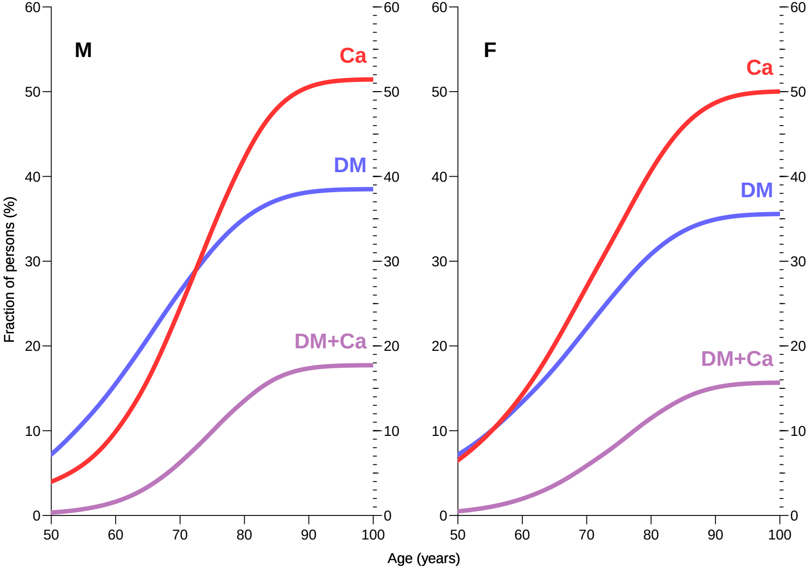
1-month transition probabilities $(\times 10^4)$ at age 66 years:

from \ to	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

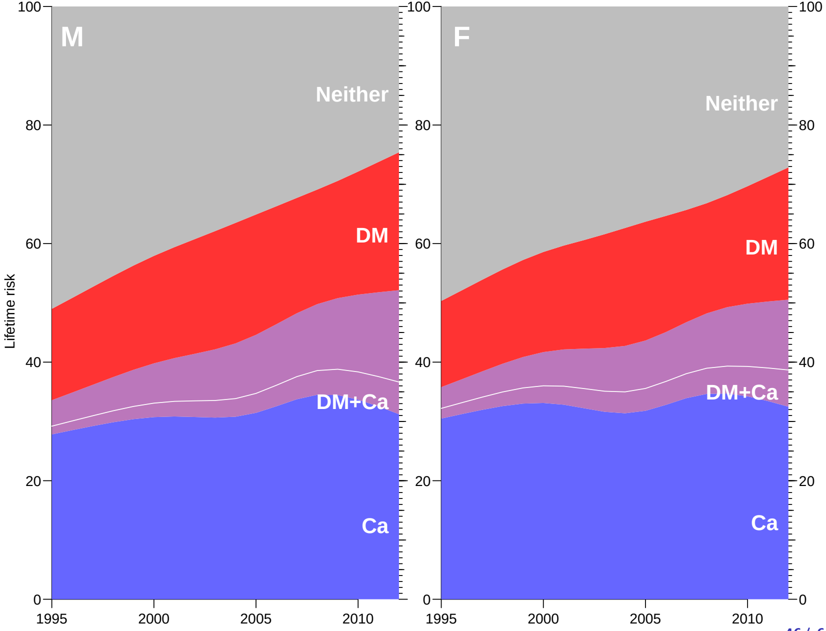
State occupancy probabilities



Lifetime risk



Trend in lifetime risk



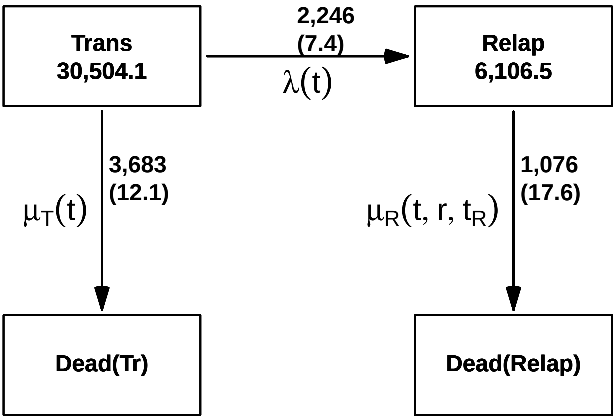
Continuous time rates

- Transition rates between states:
  - based on 1-year tabulation of data
  - age-period-cohort models
  - using smooth effects of age, period and cohort
- Assuming only one transition per interval: small intervals
- State probabilities simple closed-form function of rates
- Numerical integration of closed form functions trivial
- Matrix multiplication trivial

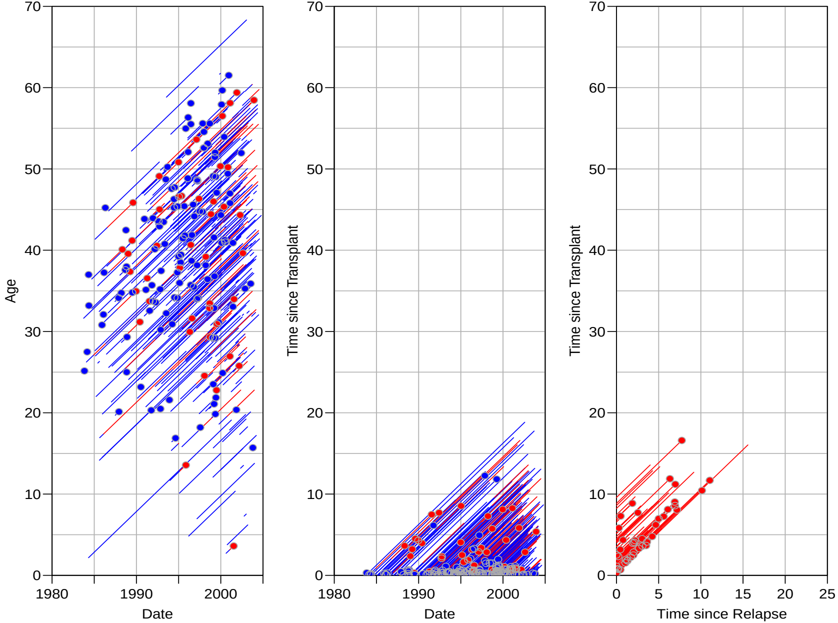
. . . simplified by a parametric form for rates as function of time

EBMT transplant data

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



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


Age
Date
Time since Transplant
Date
Time since Transplant
Time since Relapse

Markov property: Empirical question

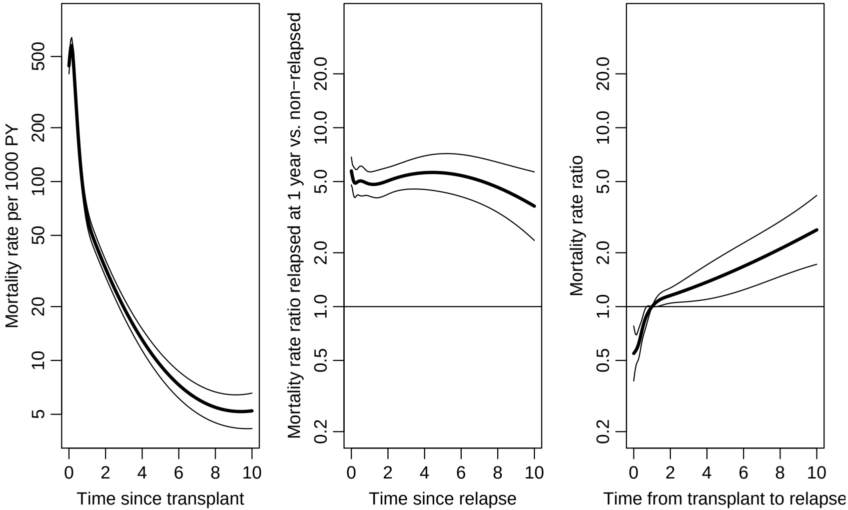
Model for mortality rates:

- t time since transplant
- r time since relapse (if relapsed)
- t_r time from transplant to relapse
- Fit the model for all transitions:
  - split follow-up time
  - fit Poisson model with covariates
  - and spline terms for each time scale.
- `Lexis` machinery from the **Epi** package for **R**
- ...for representation and manipulation of follow-up data.

Using the Lexis machinery [4, 5]

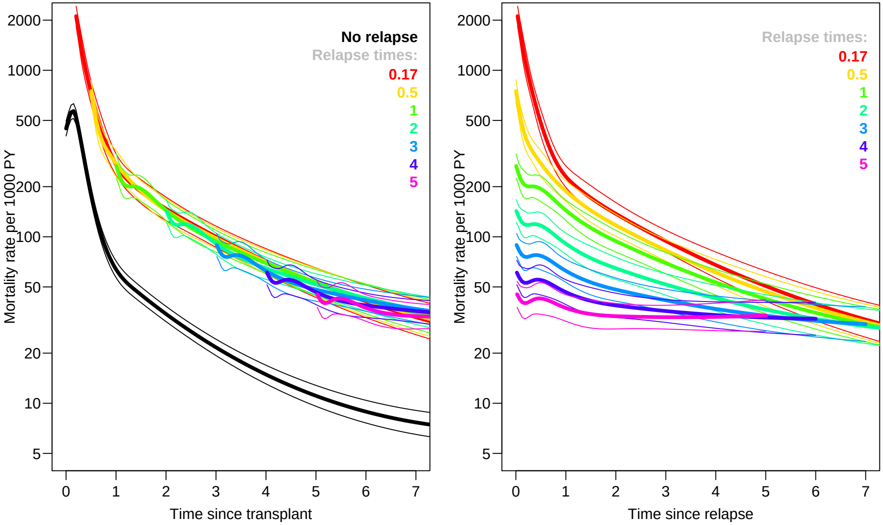
```
cmlT <- Lexis(entry = list(cal = cal.yr(dot),
                           age = cal.yr(dot)-cal.yr(dob),
                           tst = 0),
               exit = list(cal = cal.yr(dof)),
        exit.status = dead,
             states = c("Transplant","Dead"),
               data = cml )

cmlL <- cutLexis( cmlT, cut = cal.yr(cmlT$dor),
                  new.state = "Relapse",
                  new.scale = "tsr",
           precursor.states = "Transplant")

> 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  ...
151 1989.16 38.10 1.87   0    4.93   Relap    Dead  ...
```

$$\log(\mu) = h(t) + k(r) + g(t-r) + X\beta$$



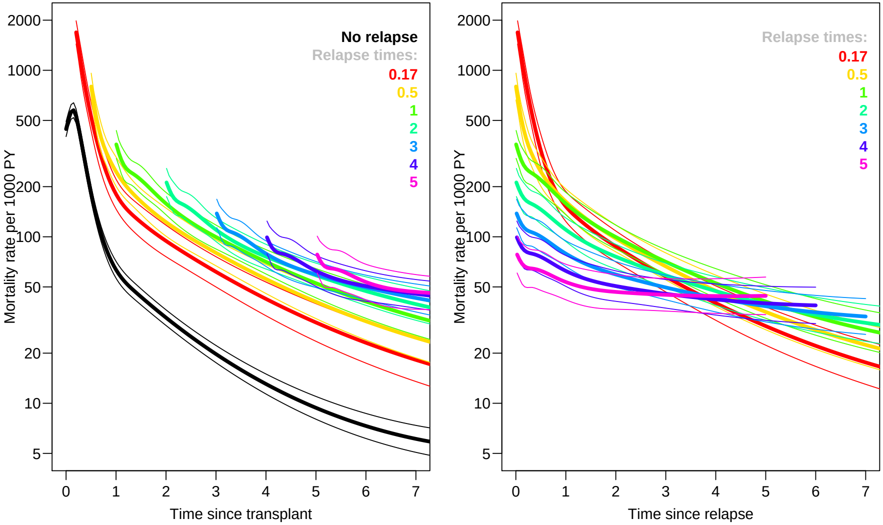
t: time since transplant $\quad$ r: time since relapse

$$\log(\mu) = h(t) + k(r) \qquad\qquad + X\beta$$



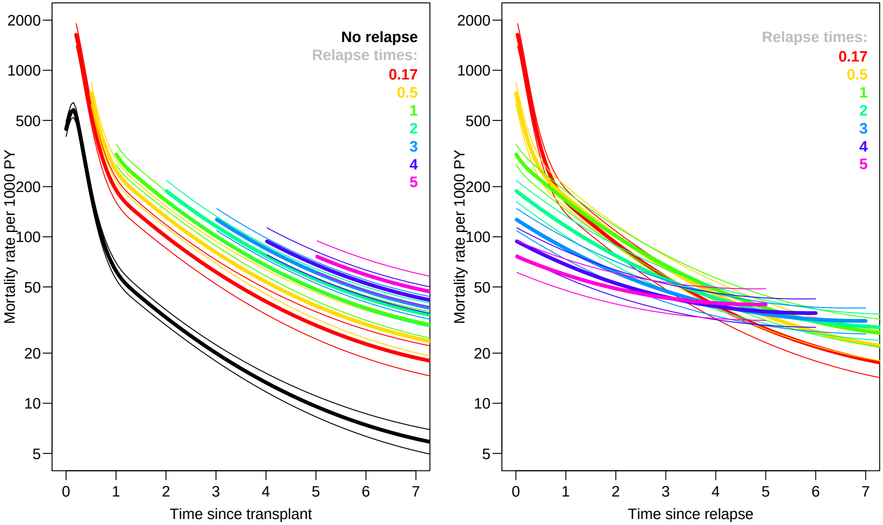
t: time since transplant $\quad r$: time since relapse

$$\log(\mu) = h(t) + k(r) + g(t - r) + X\beta$$



t: time since transplant r: time since relapse

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



t: time since transplant $\quad r$: time since relapse

Model summary

- Mortality of relapsed patients depends on **when** they relapsed.
- We also checked if the mortality depended on **time since** they relapsed.
  It did not.
- **Note:** It is an **empirical** question what timescales to use.
- **Note:** In order to compute probabilities, we need a model for the relapse rates (λ) in addition to the mortality rates (μ_T, μ_R)
- ...unfortunately not a Markov model

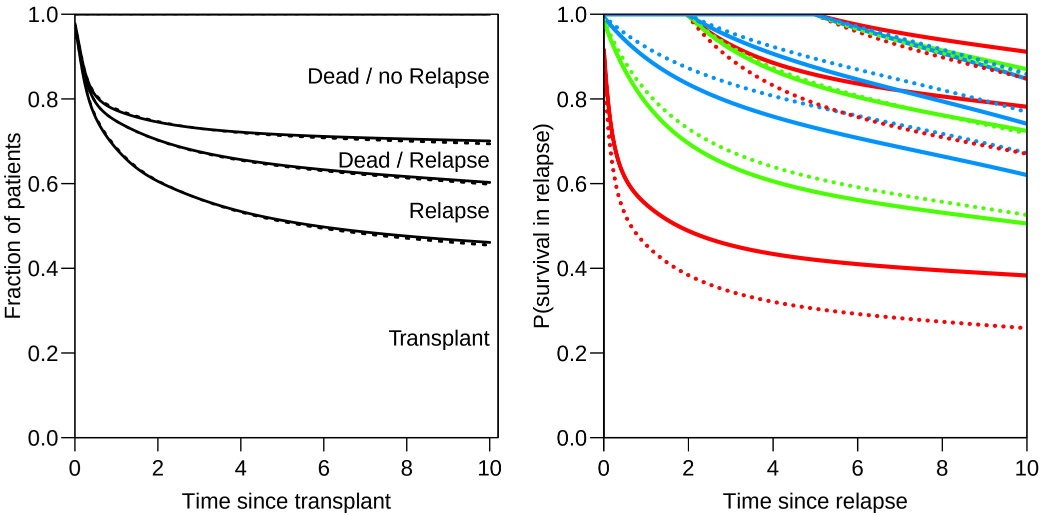
Not Markov: the hard way

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

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

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

$$\mathrm{P}\left\{\text{D(R) at } t\right\} = 1 - \mathrm{P}\left\{\text{T at } t\right\} - \mathrm{P}\left\{\text{D(T) at } t\right\} - \mathrm{P}\left\{\text{R at } t\right\}$$



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

- The world is continuous
- Time effect likely to be smooth
- A single time scale is rarely sufficient
- Different timescales require joint reporting
- Continuous time formulae easiest to handle:
  - Parametric form of time-effects allow direct implementation of probability theory
  - Choice of time scale**s** is an **empirical** problem
- Non/Semi-parametric survival model not well suited for this
- Stick to this world: Fewer tables — more graphs!

Thanks for your attention

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