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

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Inference in Multistate models

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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

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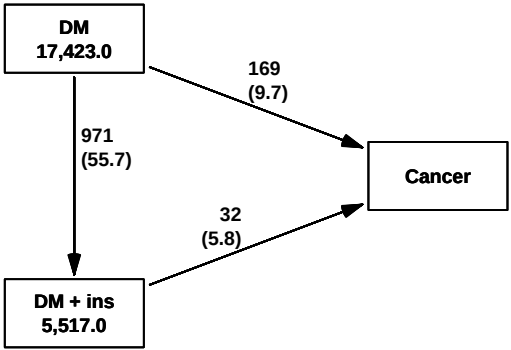
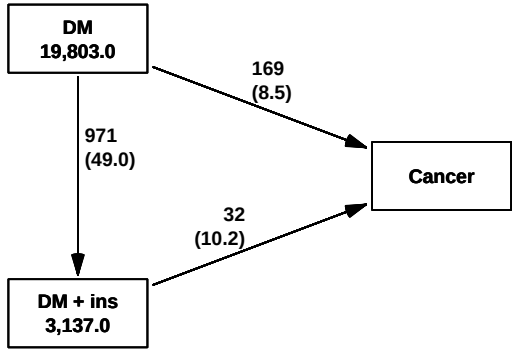
- Wrongly including persons' follow-up in the wrong state (namely the one reached some time in the future).
- Frequently caused by classification of **persons** instead of classification of **follow-up time**

Immortal time bias

Yang *et al.*:
Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry, *Diabetes*, 2010 [3]
. . . found that the RR of cancer associated with insulin use among diabetes patients were 0.22 — very small indeed.

This was challenged [4] because person-years enumeration was possible from the published tables.





$5.8/9.7 = 0.60$

$10.2/8.5 = 1.20$

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- Time is taken to be a **response** variable observed for each person
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- **Persons** classified by exposure
- The **real** unit of observation should be person-time

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- Covariates relate to each interval of follow-up
- Allows **multiple** timescales, *e.g.* age and disease duration.

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

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- Cox's approach profiles $\lambda_0(t)$ out.

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

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- Modelling is by standard `glm` Poisson

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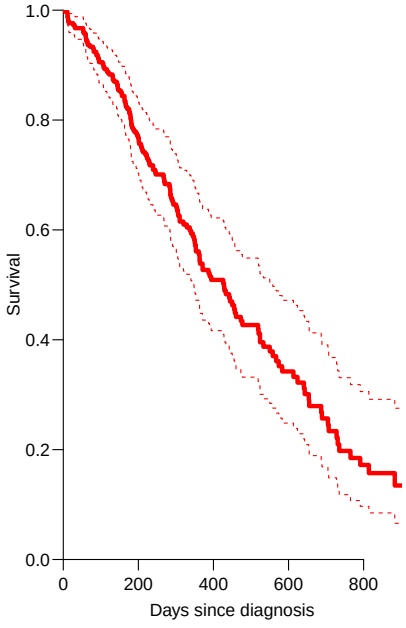
- Split data:
  - Poisson model, time as factor
  - Poisson model, time as spline

Mayo Clinic lung cancer 60 year old woman



Example: Mayo Clinic lung cancer I

```
> round( cmp, 5 )
                    age    2.5%   97.5%     sex    2.5%   97.5%
Cox             1.01716 0.99894 1.03571 0.59896 0.43137 0.83165
Poisson-factor  1.01716 0.99894 1.03571 0.59896 0.43137 0.83165
Poisson-spline  1.01619 0.99803 1.03468 0.59983 0.43199 0.83287
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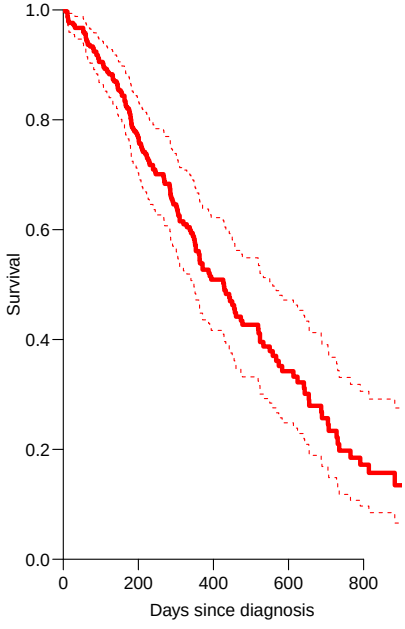
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Survival
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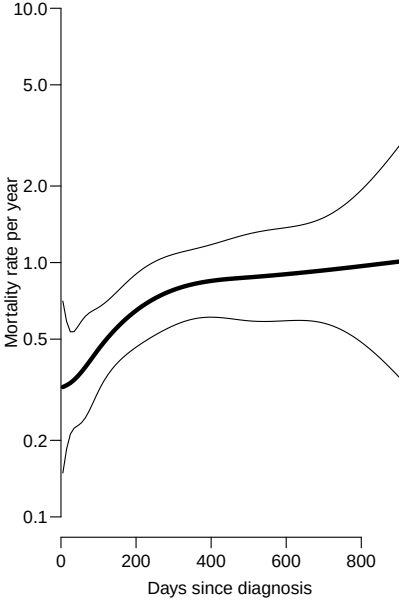
Days since diagnosis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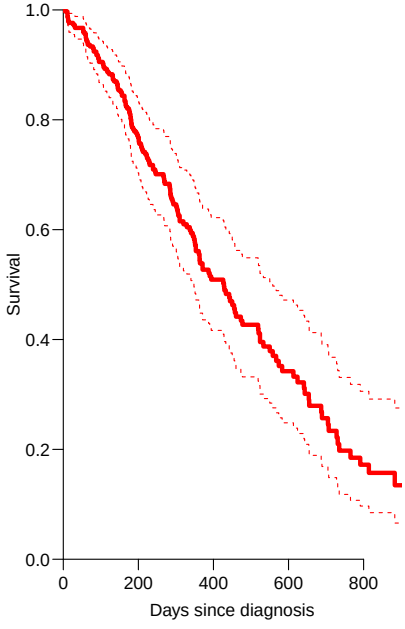
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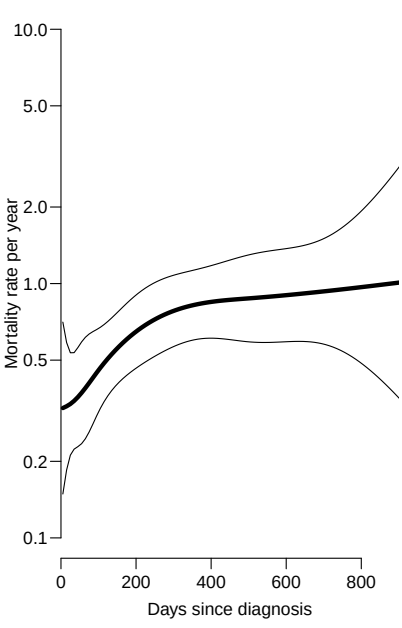
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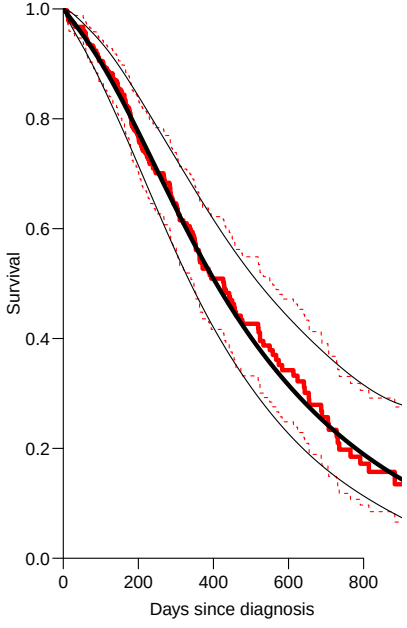
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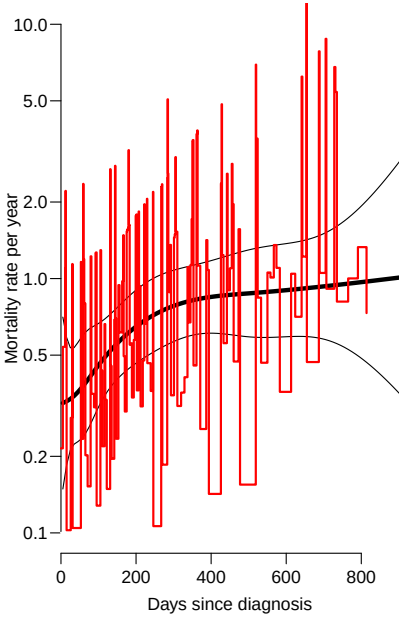
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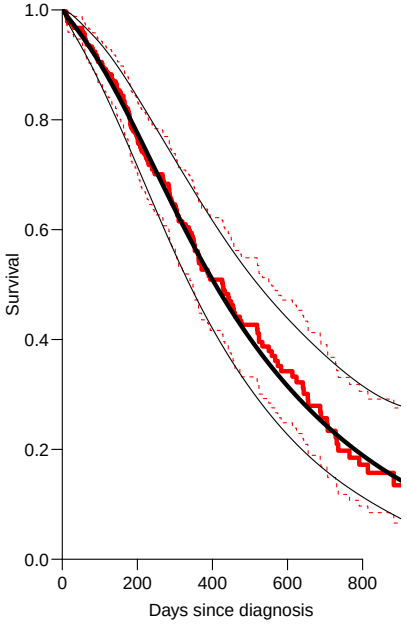
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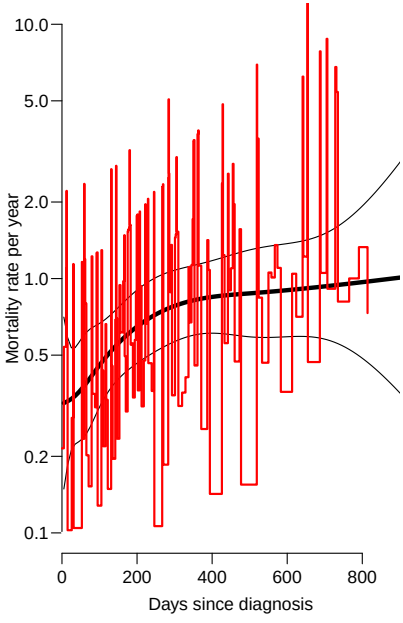
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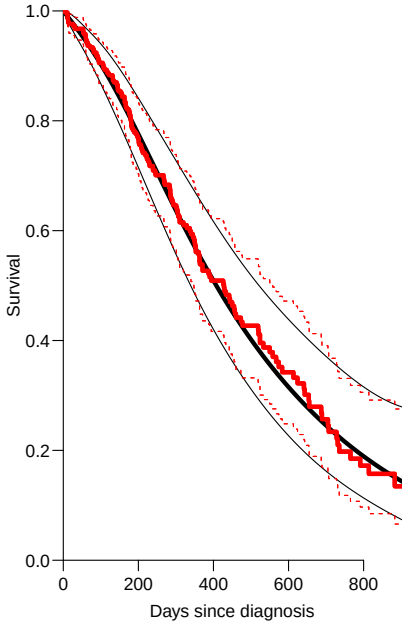
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```
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+                                  age + factor( sex ),
+                     offset = log(lex.dur),
+                     family=poisson, data=Lung.s, eps=10^-8, maxit=25 )


> 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))
```

What the Cox-model really is

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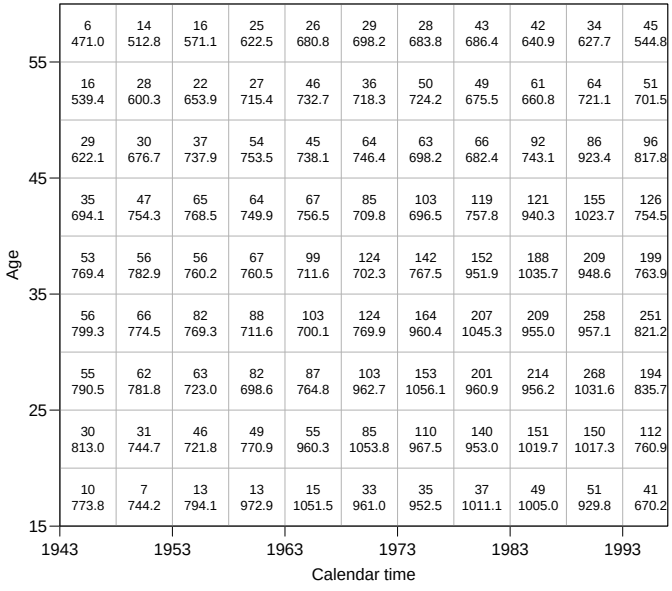
Tabulation of register data



Testis cancer cases in Denmark.

Male person-years in Denmark.

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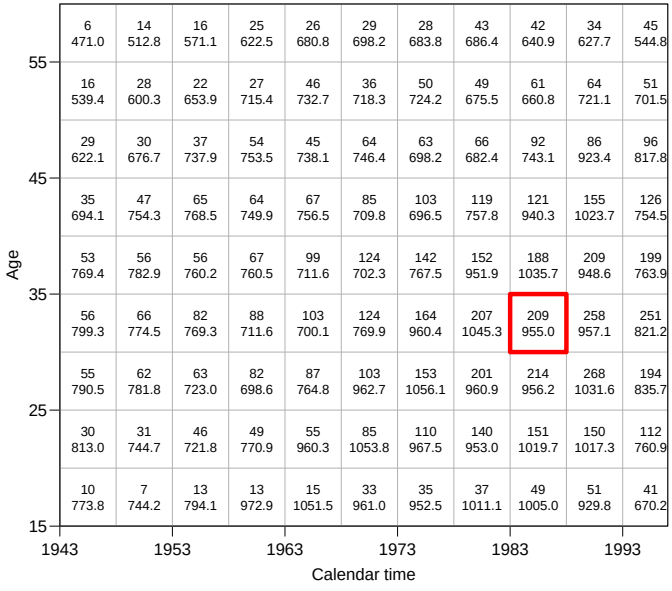

Age	1943	1953	1963	1973	1983	1993
55	6 471.0	14 512.8	16 571.1	25 622.5	26 680.8	29 698.2	28 683.8	43 686.4	42 640.9	34 627.7	45 544.8
45	16 539.4	28 600.3	22 653.9	27 715.4	46 732.7	36 718.3	50 724.2	49 675.5	61 660.8	64 721.1	51 701.5
35	29 622.1	30 676.7	37 737.9	54 753.5	45 738.1	64 746.4	63 698.2	66 682.4	92 743.1	86 923.4	96 817.8
25	35 694.1	47 754.3	65 768.5	64 749.9	67 756.5	85 709.8	103 696.5	119 757.8	121 940.3	155 1023.7	126 754.5
15	53 769.4	56 782.9	56 760.2	67 760.5	99 711.6	124 702.3	142 767.5	152 951.9	188 1035.7	209 948.6	199 763.9
	56 799.3	66 774.5	82 769.3	88 711.6	103 700.1	124 769.9	164 960.4	207 1045.3	209 955.0	258 957.1	251 821.2
	55 790.5	62 781.8	63 723.0	82 698.6	87 764.8	103 962.7	153 1056.1	201 960.9	214 956.2	268 1031.6	194 835.7
	30 813.0	31 744.7	46 721.8	49 770.9	55 960.3	85 1053.8	110 967.5	140 953.0	151 1019.7	150 1017.3	112 760.9
	10 773.8	7 744.2	13 794.1	13 972.9	15 1051.5	33 961.0	35 952.5	37 1011.1	49 1005.0	51 929.8	41 670.2

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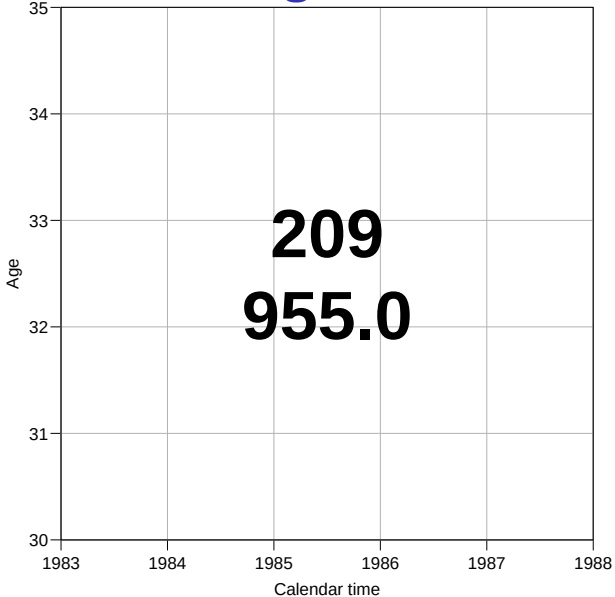

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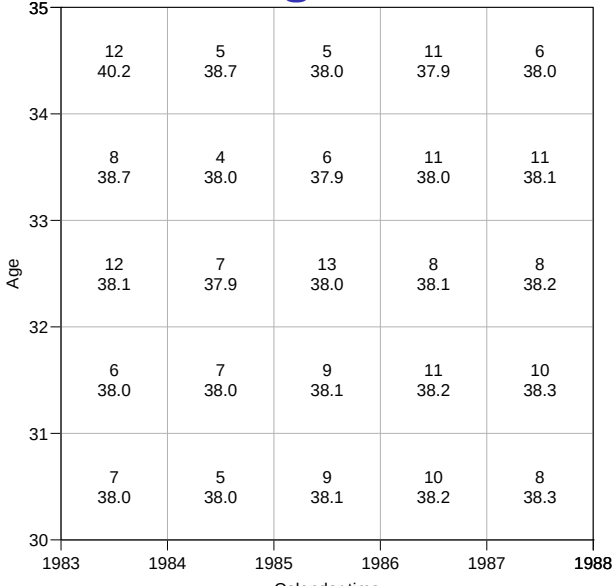

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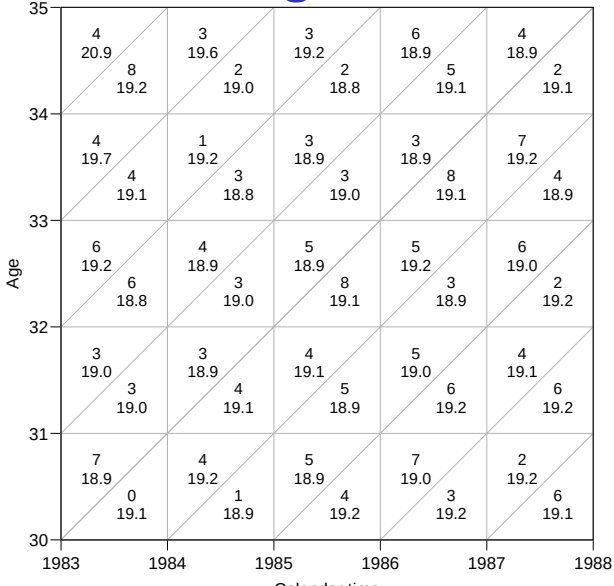

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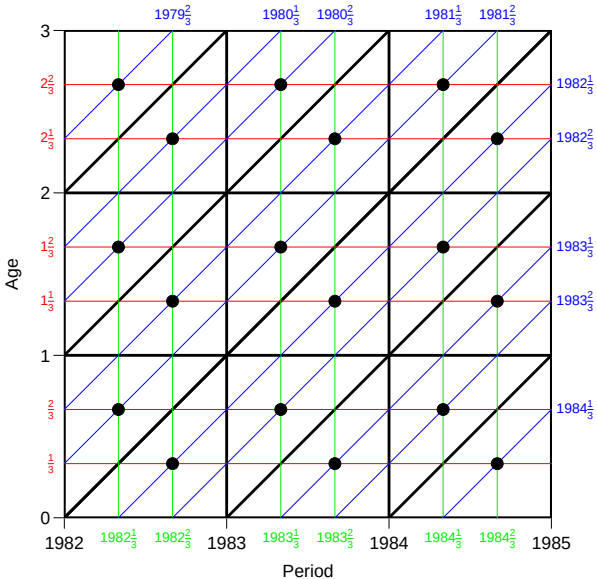
Male person-years in Denmark.

Subdivision by year of birth (cohort).

Tabulation by age, period and cohort



Gives triangular sets with differing mean age, period and cohort:

These correct midpoints for age, period and cohort must be used in modelling.

Model for triangular data

- One parameter per distinct value on each timescale.

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- . . . only 26 parameters identifiable.

Problem: Disconnected design!

Log-likelihood contribution from one triangle:

$$D_{ap}\log(\lambda_{ap}) - \lambda_{ap}\, Y_{ap} = D_{ap}(\alpha_a + \beta_p + \gamma_c) - \exp(\alpha_a + \beta_p + \gamma_c)\, Y_{ap}$$

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$$\sum_{a,p \in \triangledown} D_{ap}\log(\lambda_{ap}) - \lambda_{ap}\, Y_{ap} + \sum_{a,p \in \triangle} D_{ap}\log(\lambda_{ap}) - \lambda_{ap}\, Y_{ap}$$

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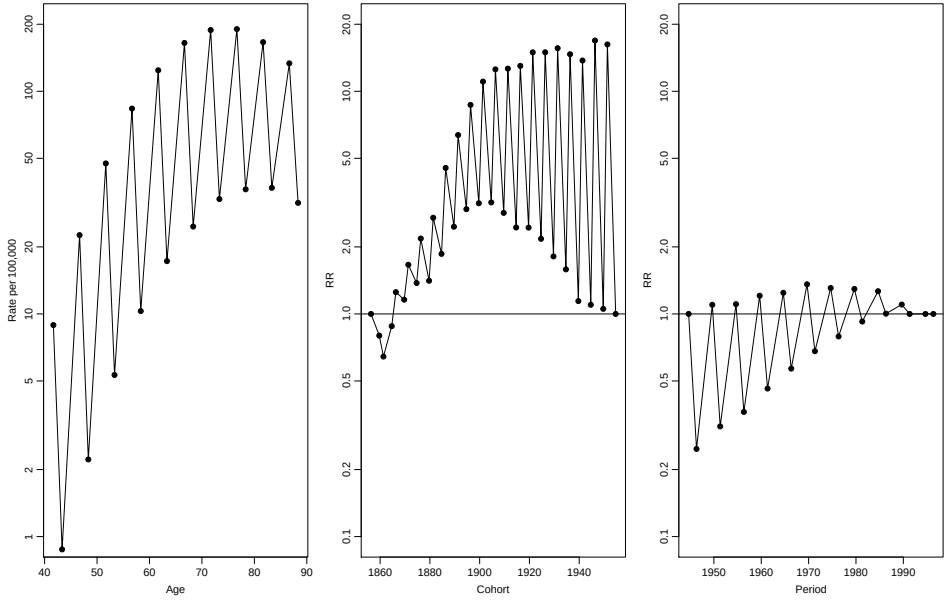
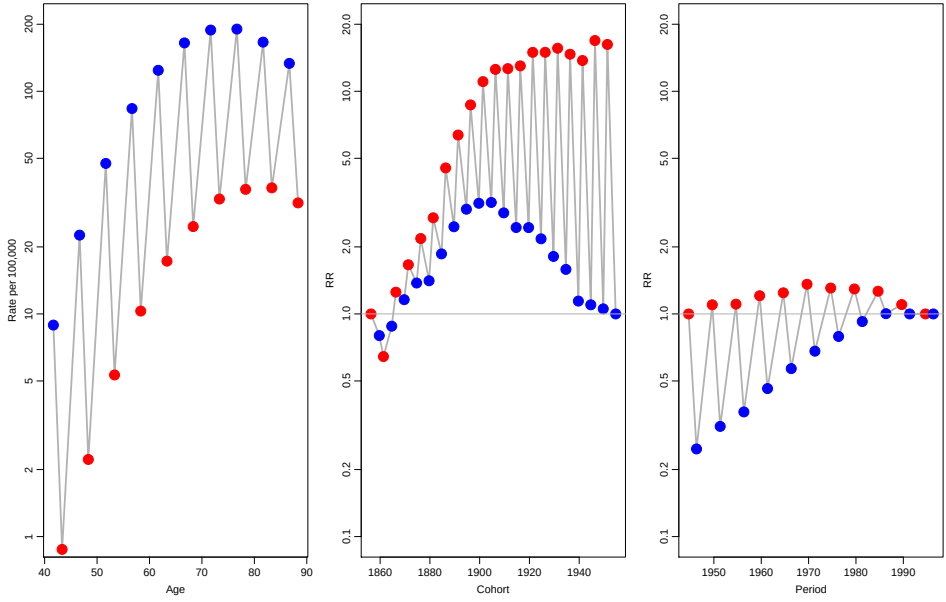
No common parameters between terms — two separate models:
One for upper triangles, one for lower.

Illustration by Danish lung cancer data

```
> library( Epi )
> data( lungDK )
> lungDK[1:10,]
   A5   P5   C5 up       Ax       Px       Cx  D        Y
1  40 1943 1898  1 43.33333 1944.667 1901.333 52 336233.8
2  40 1943 1903  0 41.66667 1946.333 1904.667 28 357812.7
3  40 1948 1903  1 43.33333 1949.667 1906.333 51 363783.7
4  40 1948 1908  0 41.66667 1951.333 1909.667 30 390985.8
5  40 1953 1908  1 43.33333 1954.667 1911.333 50 391925.3
6  40 1953 1913  0 41.66667 1956.333 1914.667 23 377515.3
7  40 1958 1913  1 43.33333 1959.667 1916.333 56 365575.5
8  40 1958 1918  0 41.66667 1961.333 1919.667 43 383689.0
9  40 1963 1918  1 43.33333 1964.667 1921.333 44 385878.5
10 40 1963 1923  0 41.66667 1966.333 1924.667 38 371361.5
```


Rate per 100,000
200
100
50
20
10
5
2
1
40
50
60
70
80
90
Age
RR
20.0
10.0
5.0
2.0
1.0
0.5
0.2
0.1
1860
1880
1900
1920
1940
Cohort
RR
20.0
10.0
5.0
2.0
1.0
0.5
0.2
0.1
1950
1960
1970
1980
1990
Period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200
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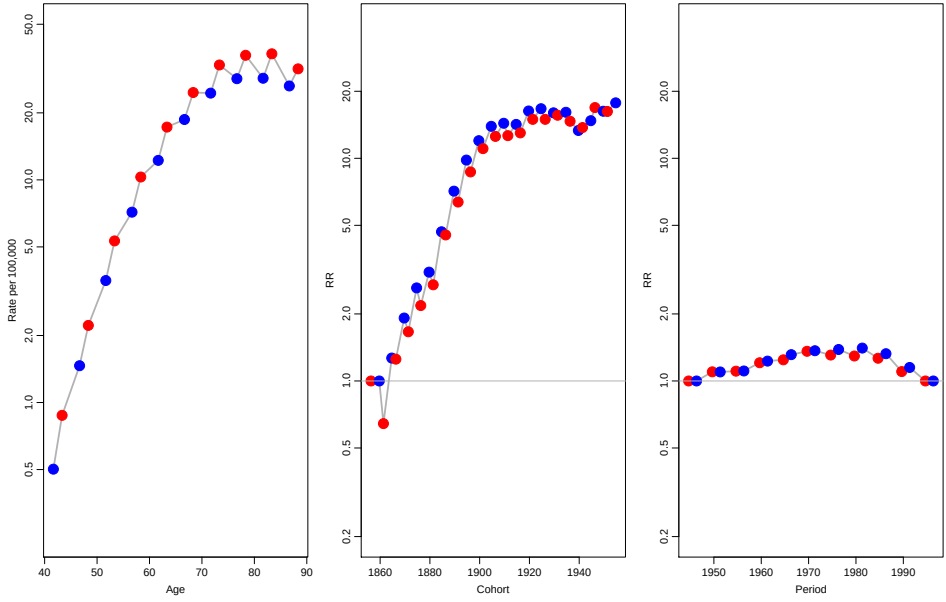
RR
20.0
10.0
5.0
2.0
1.0
0.5
0.2
0.1
1950
1960
1970
1980
1990
Period

Now, separately fit models for upper and lower triangles:

```
> mx.u <- glm( D ~ factor(Ax) - 1 +
+                 factor(Cx) +
+                 factor(Px) + offset( log( Y/10^5 ) ), family=poisson,
+                 data=lungDK[lungDK$up==1,] )
> mx.l <- glm( D ~ factor(Ax) - 1 +
+                 factor(Cx) +
+                 factor(Px) + offset( log( Y/10^5 ) ), family=poisson,
+                 data=lungDK[lungDK$up==0,] )
> mx$deviance
[1] 284.7269
> mx.l$deviance
[1] 134.4566
> mx.u$deviance
[1] 150.2703
> mx.l$deviance+mx.u$deviance
[1] 284.7269
```


Rate per 100,000
0.5
1.0
2.0
5.0
10.0
20.0
50.0
40
50
60
70
80
90
Age
RR
0.2
0.5
1.0
2.0
5.0
10.0
20.0
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- Fixes the problem with non-equidistant age, period and cohort classes
- The practical problem is how to choose a reasonable parametrization of these functions, and how to get estimates,

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$$\begin{aligned}
\lambda_{ap} &= f(a) + g(p) + h(c) \\
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&= f(a) - \mu_a - \gamma a + \\
&\quad g(p) + \mu_a + \mu_c + \gamma p + \\
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. . . and is alien to the chosen parametrization of the APC-effects

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3. The period function is 0 on average with 0 slope, interpretable as log-RR relative to the age-cohort prediction. (residual log-RR).

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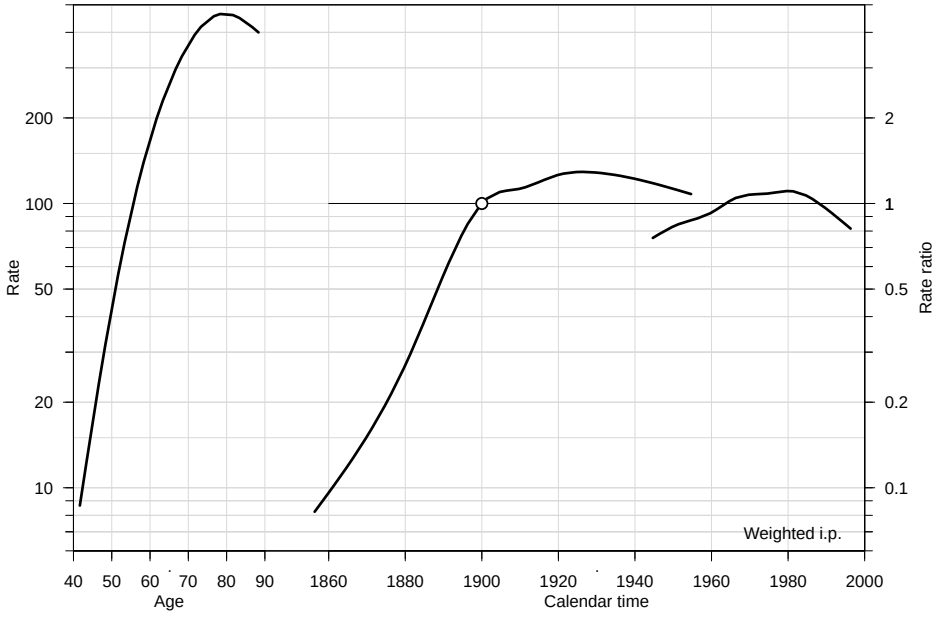
4. Extracting trend requires an **inner product** to project colums of $g(p)$ on the orthogonal of $(1 \vdots p)$, in the literature implicitly assumed to be induced by the identity, — a bold assumption

How to?

Implemented in `apc.fit` in the `Epi` package

```
m1 <- apc.fit( A=lungDK$Ax,
               P=lungDK$Px,
               D=lungDK$D,
               Y=lungDK$Y/10^5,
           ref.c=1900 )
apc.plot( m1 )
```

Consult the help page for details.


Rate
200
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Rate ratio
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1
0.5
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Rate
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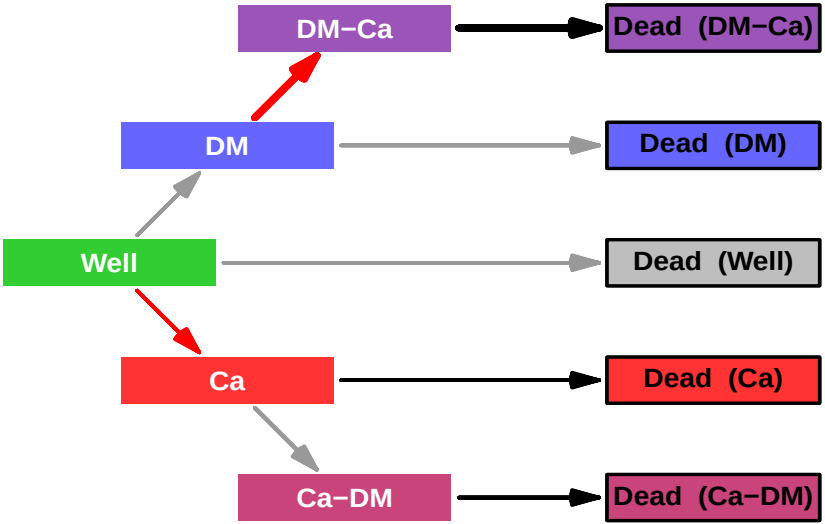
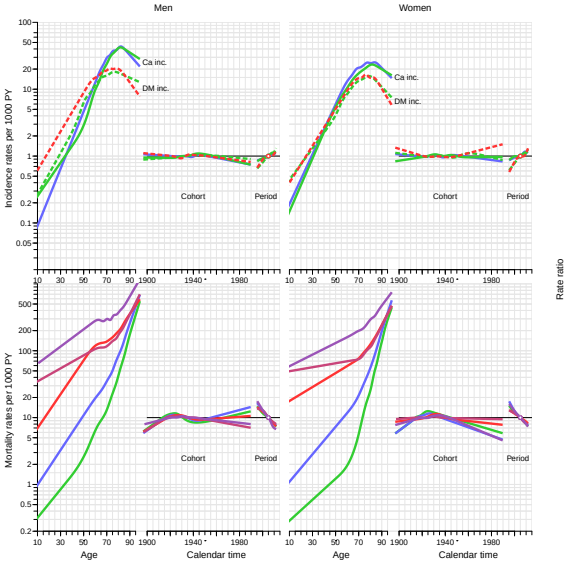
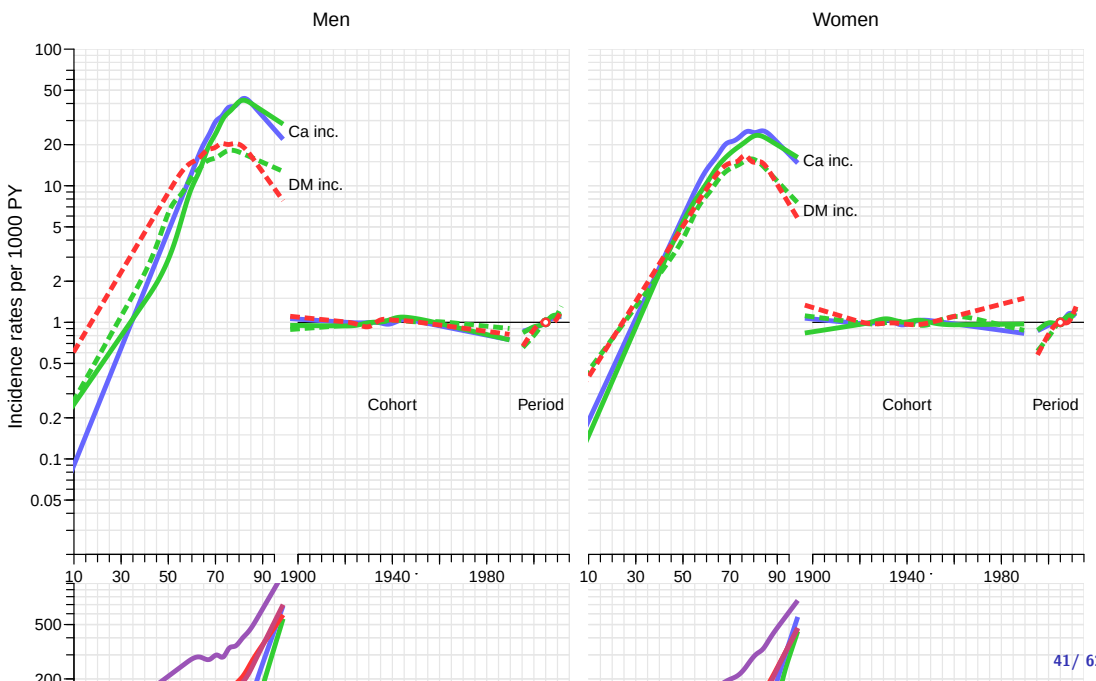
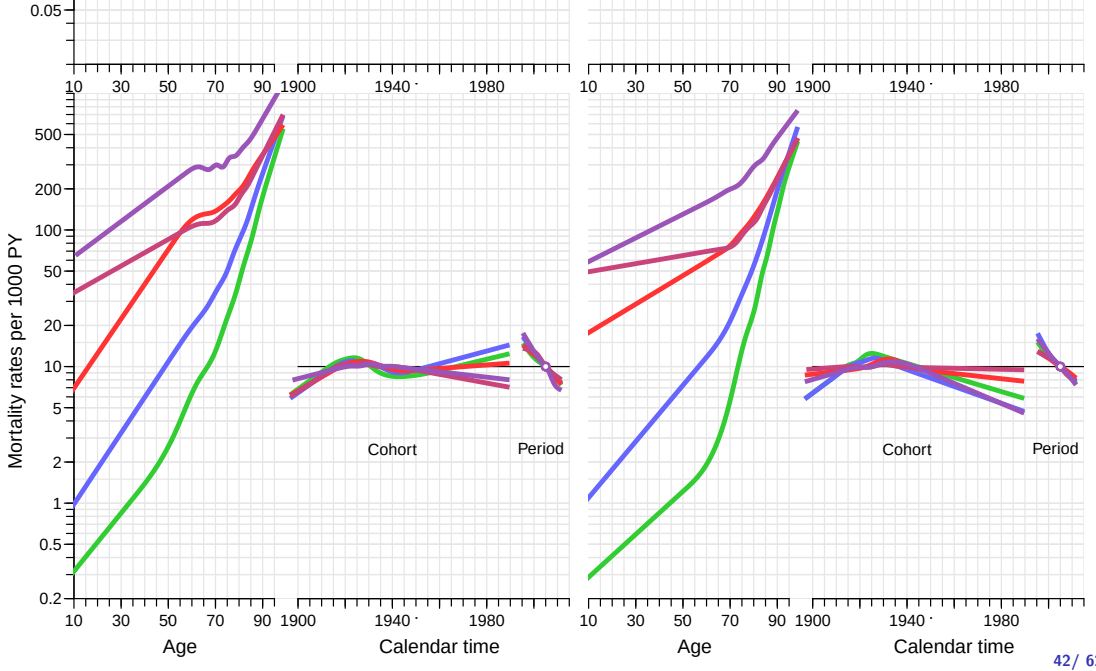
Joint occurrence of Diabetes and Cancer



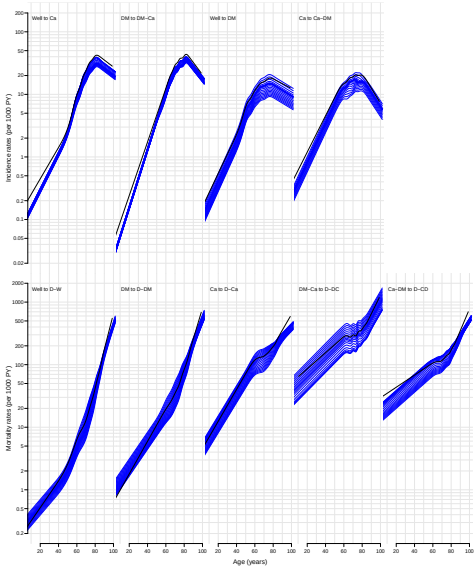
Joint occurrence of Diabetes and Cancer

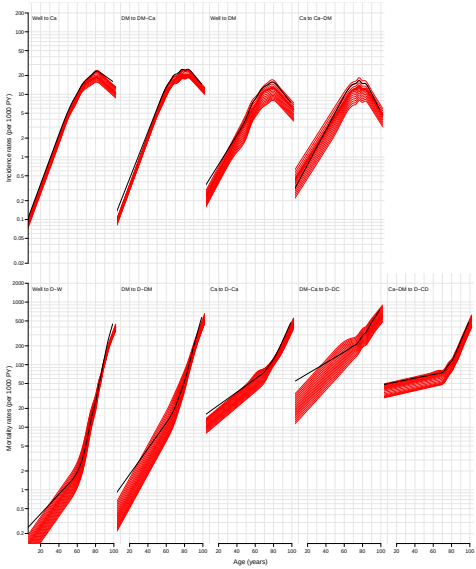



Men
Women
Incidence rates per 1000 PY
100
50
20
10
5
2
1
0.5
0.2
0.1
0.05
Ca inc.
DM inc.
Cohort
Period
10
30
50
70
90
1900
1940
1980
500
200


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
Age
Calendar time
Cohort
Period

Predicted rates — cross-sectional 1995–2010





Continuous rates

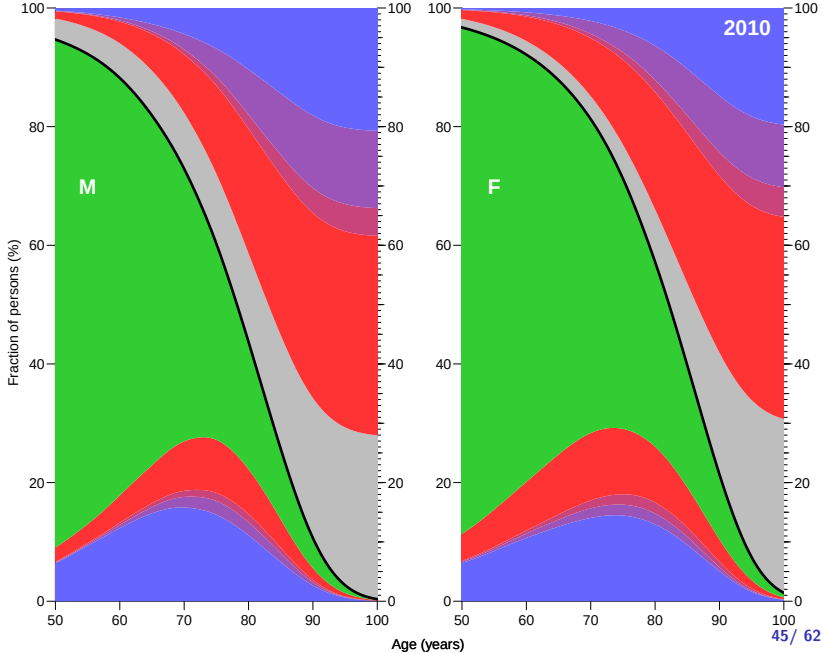
1-month cumulative rates $\rightarrow$ transition probabilities

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

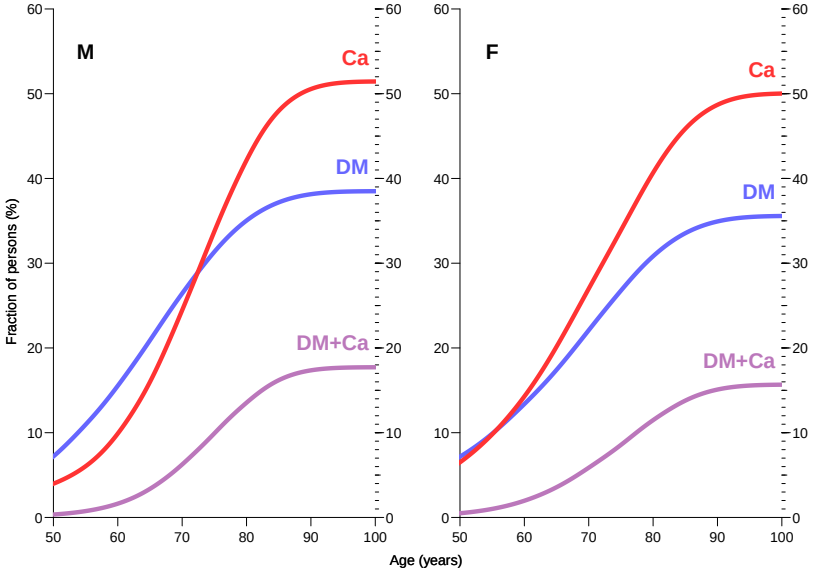
1-month transition probabilities ($\times 10^4$) at age 66 years:

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

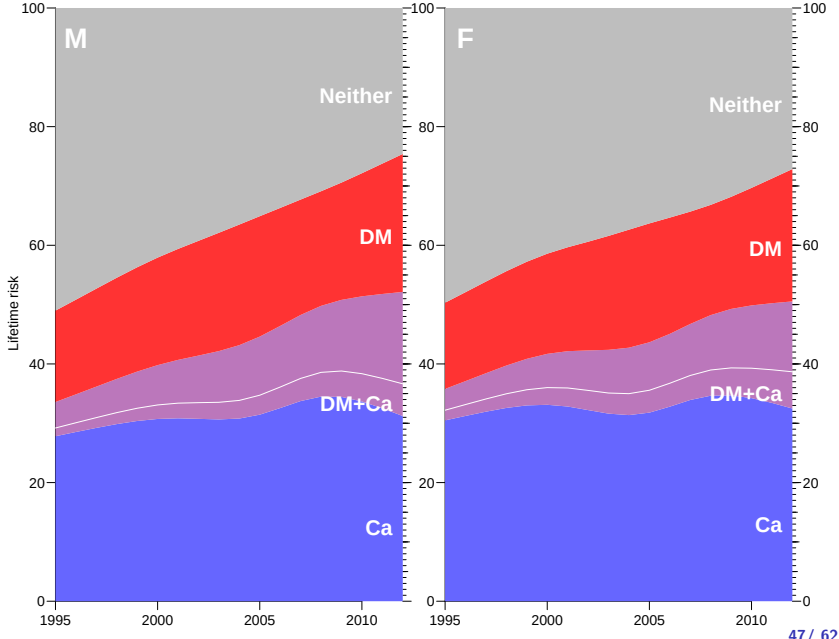
State occupancy probabilities



Lifetime risk



Trend in lifetime risk



Continuous time rates

- Transition rates between states:

Continuous time rates

- Transition rates between states:
  - based on 1-year tabulation of data

Continuous time rates

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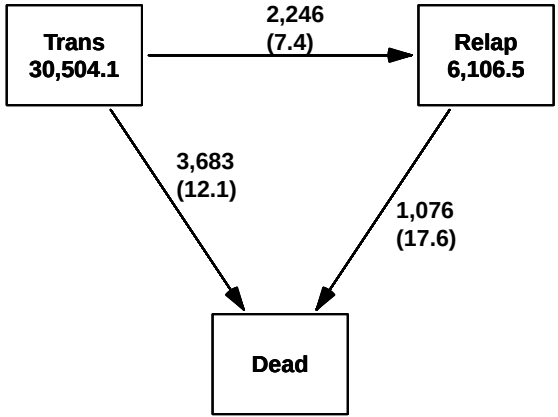
All simplified by a parametric form for rates as function of time

EBMT transplant data

Iacobelli & Carstensen: Multistate Models with Multiple Timescales, Stat Med 2013, [5]



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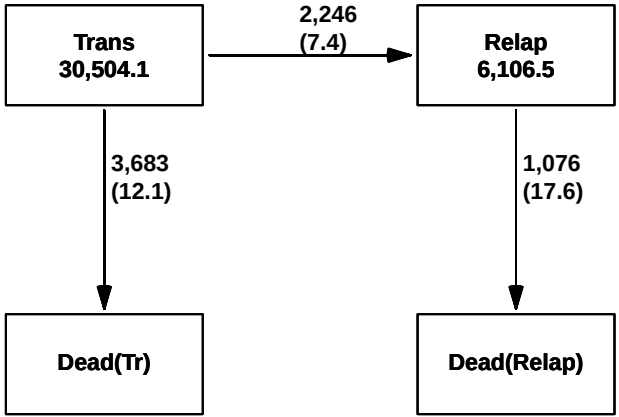

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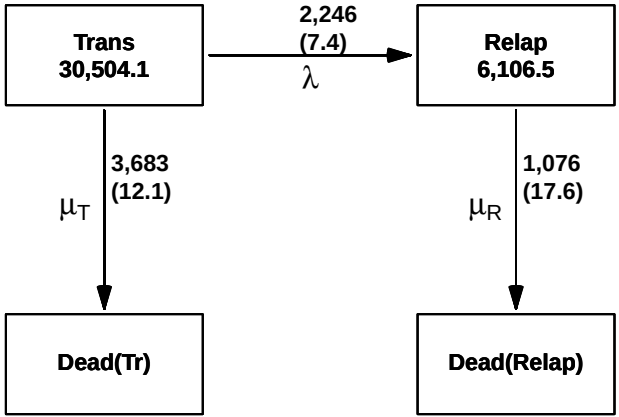

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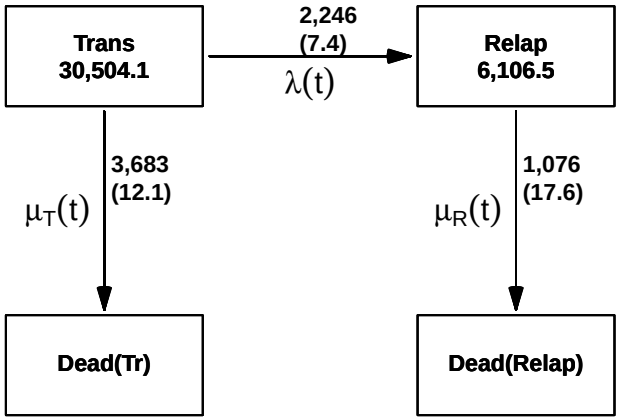

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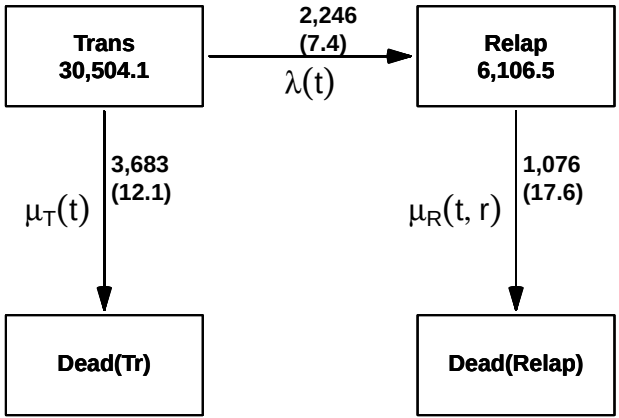

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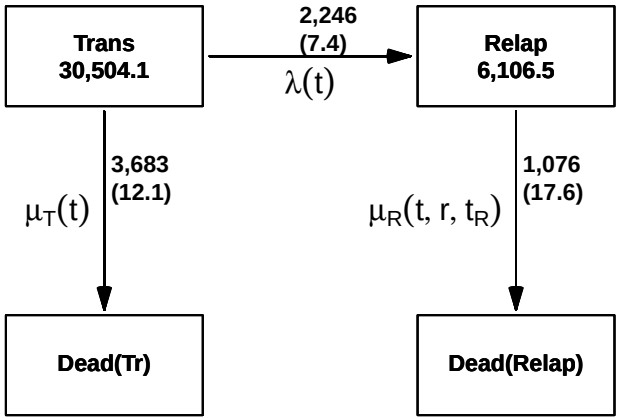

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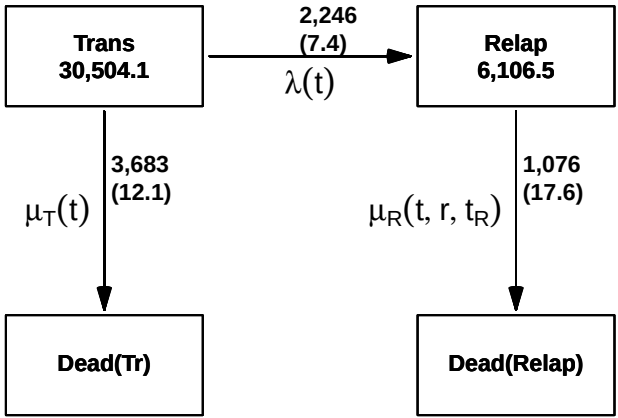
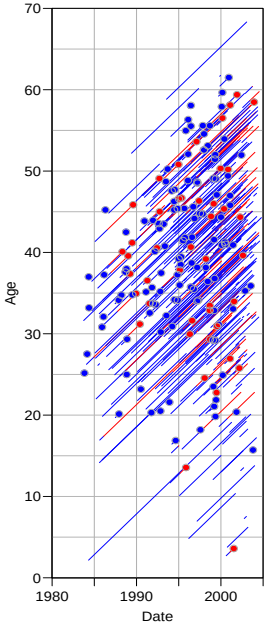
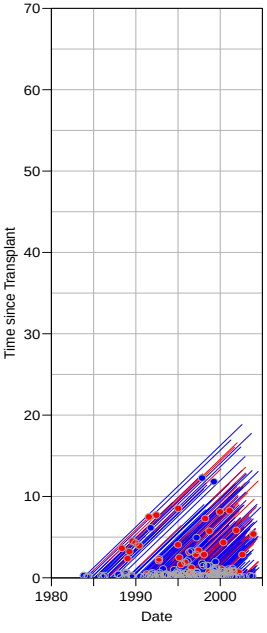
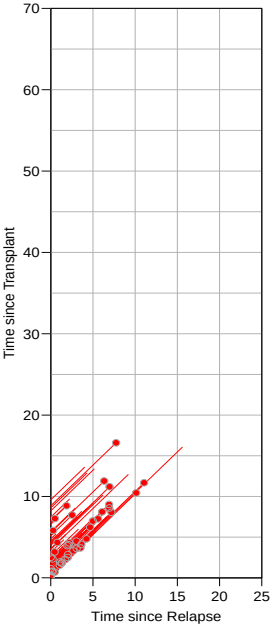


other covariates: Age and date at Tx, sex, donor type, CML type


Age
Date
0
10
20
30
40
50
60
70
1980
1990
2000


Time since Transplant
Date
0
10
20
30
40
50
60
70
1980
1990
2000


Time since Transplant
Time since Relapse
0
10
20
30
40
50
60
70
0
5
10
15
20
25

Markov property: Empirical question

Model for mortality rates:

- t time since transplant

Markov property: Empirical question

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- t time since transplant
- r time since relapse (if relapsed)

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

Using the Lexis machinery [6, 7]

```
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  ...
```

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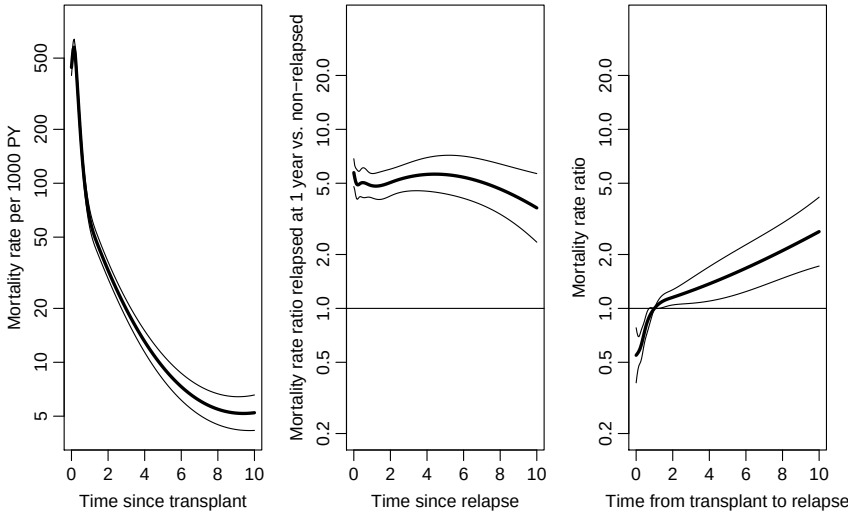
$$\log(\mu) = h(t) + k(r) + g(t - r) + X\beta$$



t: time since transplant r: time since relapse

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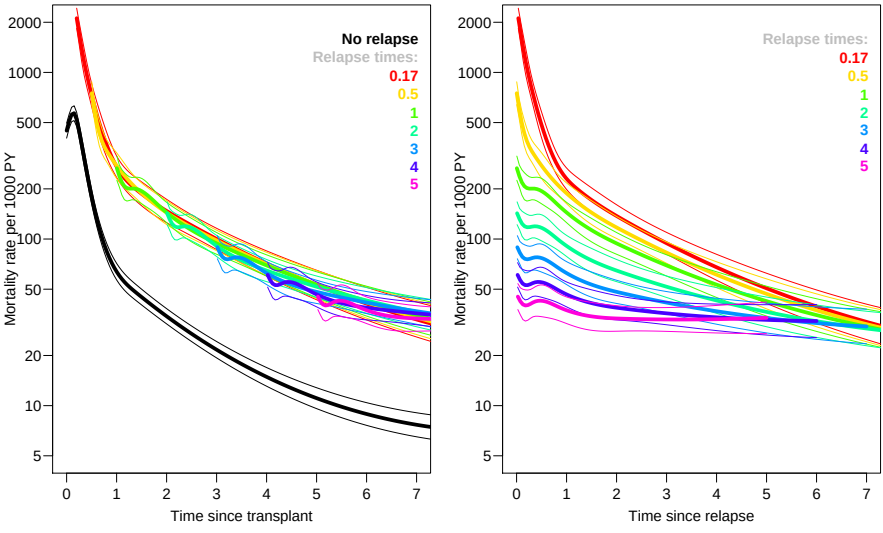

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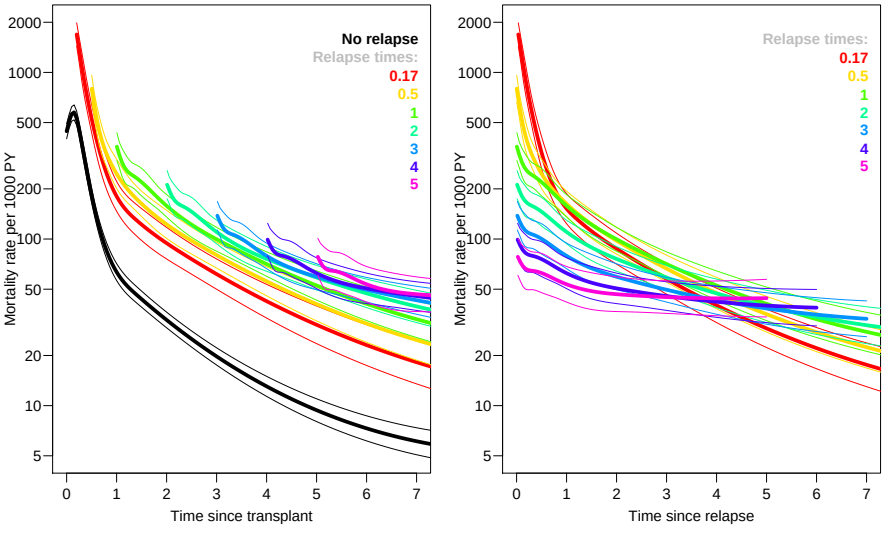

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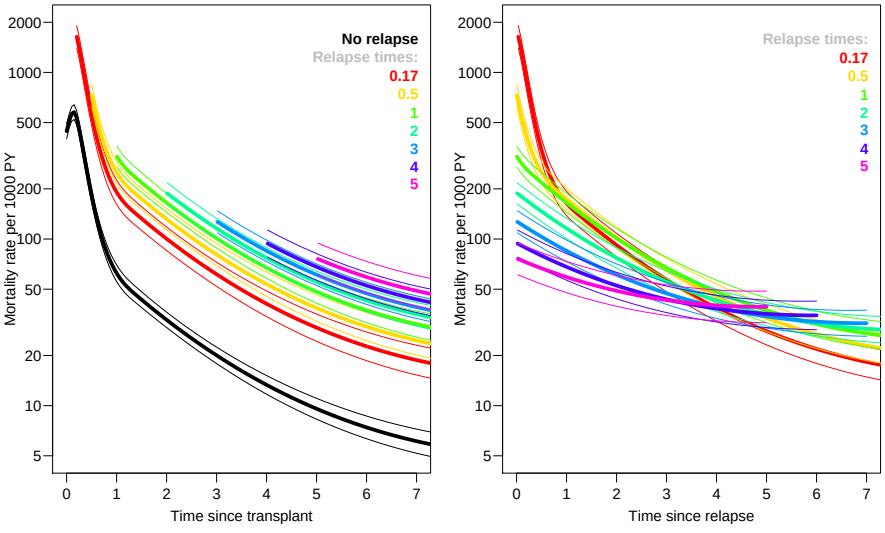

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- . . . unfortunately not a Markov model

Not Markov: the hard way

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

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

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

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

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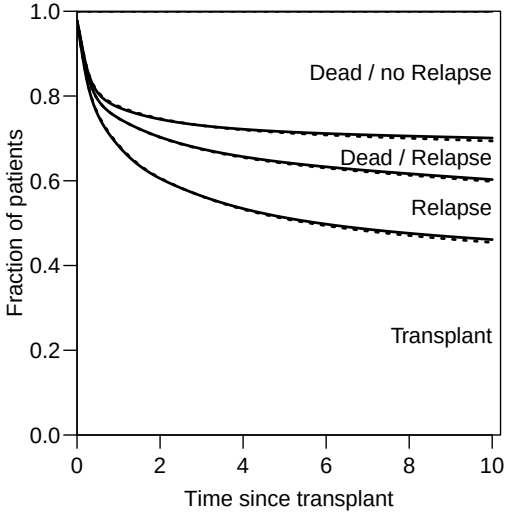
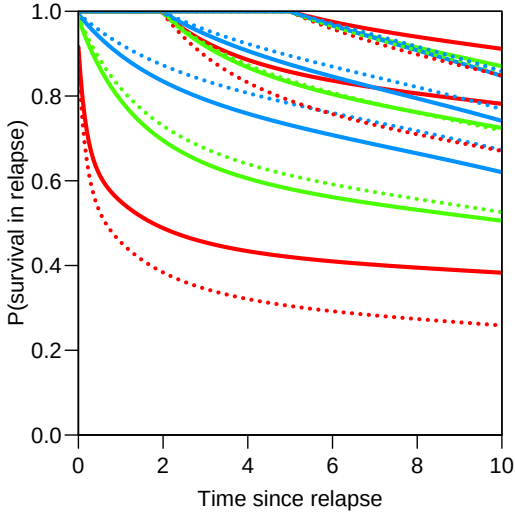
$$\mathrm{P}\{\mathsf{D(R)\ at}\ t\} = 1 - \mathrm{P}\{\mathsf{T\ at}\ t\} - \mathrm{P}\{\mathsf{D(T)\ at}\ t\} - \mathrm{P}\{\mathsf{R\ at}\ t\}$$





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

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Thanks for your attention

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