3.24pt

Multistate models:

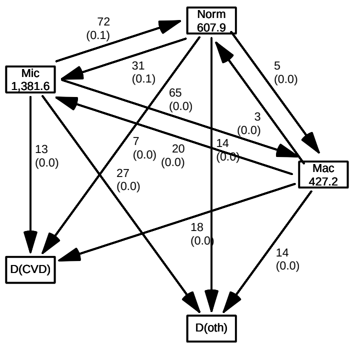
Occurrence rates, cumulative risks, competing risks, state probabilities with multiple states and time scales in Register Research with R and `Epi::Lexis`

Bendix Carstensen Steno Diabetes Center Copenhagen
Herlev, Denmark
http://BendixCarstensen.com

Aalborg Math, 7–8 March 2022

From C:\Bendix\teach\AdvCoh\courses\Aalborg.2022\slides/slides.tex Sunday 6th March, 2022, 00:38

A multistate model



A multistate model

- Not really a model
- What is the data:
  - Sequence of transitions: (when, from, to)
    ...same as:
  - sequence of: (state time, next state)
- What are the target parameters:
  - Rates (the arrows)
  - State probabilities (of being in a state at a given time)
  - Survival probability
  - Sojourn times (how long time do you spend in a state)
  - Probability of ever visiting a state

What is a statistical model

- Specification of a statistical machinery that could have generated data
- ...so when we have a statistical model we can simulate a data set
- The basis for th elikelihood of data is the statistical model
  ⇒ Estimation of parameters in the model
- Parameter estimates needed for prediction of rates (hazards)

Prerequisites

```
> library(Epi)
> library(popEpi)
> # popEpi::splitMulti returns a data.frame rather than a data.table
> options("popEpi.datatable" = FALSE)
```


The `lung` data set

```
> library(survival)
> data(lung)
> lung$sex <- factor(lung$sex,
+                    levels = 1:2,
+                    labels = c("M", "W"))
> lung$time <- lung$time / (365.25/12)
> head(lung)
  inst      time status age sex ph.ecog ph.karno pat.karno meal.cal wt.loss
1    3 10.053388      2  74   M       1       90       100     1175      NA
2    3 14.948665      2  68   M       0       90        90     1225      15
3    3 33.182752      1  56   M       0       90        90       NA      15
4    5  6.899384      2  57   M       1       90        60     1150      11
5    1 29.010267      2  60   M       0      100        90       NA       0
6   12 33.577002      1  74   M       1       50        80      513       0
```


Survival function

- Use `survfit` to construct the Kaplan-Meier estimator of overall survival:

```
> ?Surv
> ?survfit
> km <- survfit(Surv(time, status == 2) ~ 1, data = lung)
> km
Call: survfit(formula = Surv(time, status == 2) ~ 1, data = lung)

       n events median 0.95LCL 0.95UCL
[1,] 228    165   10.2    9.36    11.9
> # summary(km) # very long output
```


We can plot the survival curve—this is the default plot for a `survfit` object:

```
> plot(km)
```

What is the median survival? What does it mean? Explore if survival patterns between men and women are different:

```
> kms <- survfit(Surv(time, status == 2) ~ sex, data = lung)
> kms
Call: survfit(formula = Surv(time, status == 2) ~ sex, data = lung)

        n events median 0.95LCL 0.95UCL
sex=M 138    112   8.87    6.97    10.2
sex=W  90     53  14.00   11.43    18.1
```


We see that men have worse survival than women, but they are also a bit older (`age` is age at diagnosis of lung cancer):

```
> with(lung, tapply(age, sex, mean))
       M        W
63.34058 61.07778
```

Formally there is a significant difference in survival between men and women

```
> survdiff(Surv(time, status==2) ~ sex, data = lung)
Call:
survdiff(formula = Surv(time, status == 2) ~ sex, data = lung)

        N Observed Expected (O-E)^2/E (O-E)^2/V
sex=M 138      112     91.6      4.55      10.3
sex=W  90       53     73.4      5.68      10.3

 Chisq= 10.3  on 1 degrees of freedom, p= 0.001
```

Rates and rate-ratios

- Occurrence **rate**:

$$\lambda(t) = \lim_{h \to 0} \mathrm{P}\left\{\text{event in } (t, t+h] \mid \text{alive at } t\right\}/h$$

—measured in probability per time: time^{-1}
- observation in a survival study: (exit status, time alive)
- empirical rate $(d, y) = (\text{deaths}, \text{time})$
- the Cox model is a model for rates as function of time (t) and covariates (x_1, x_2):

$$\lambda(t, x) = \lambda_0(t)\exp(\beta_1 x_1 + \beta_2 x_2)$$

—mortality depends on the person's sex and age, say.
- Data looks like data for a K-M analysis **plus** covariate values

Rates and rate-ratios: Simple Cox model

Now explore how sex and age (at diagnosis) influence the mortality—note that in a Cox-model we are addressing the mortality rate and not the survival:

```
> c0 <- coxph(Surv(time, status == 2) ~ sex      , data = lung)
> c1 <- coxph(Surv(time, status == 2) ~ sex + age, data = lung)
> summary(c1)
> ci.exp(c0)
> ci.exp(c1)
```

What variables from `lung` are we using?


```
> c0 <- coxph(Surv(time, status == 2) ~ sex      , data = lung)
> c1 <- coxph(Surv(time, status == 2) ~ sex + age, data = lung)
> summary(c1)
Call:
coxph(formula = Surv(time, status == 2) ~ sex + age, data = lung)

  n= 228, number of events= 165

          coef exp(coef)  se(coef)      z Pr(>|z|)
sexW -0.513219  0.598566  0.167458 -3.065  0.00218 **
age   0.017045  1.017191  0.009223  1.848  0.06459 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

     exp(coef) exp(-coef) lower .95 upper .95
sexW    0.5986     1.6707    0.4311    0.8311
age     1.0172     0.9831    0.9990    1.0357

Concordance= 0.603  (se = 0.025 )
Likelihood ratio test= 14.12  on 2 df,   p=9e-04
Wald test            = 13.47  on 2 df,   p=0.001
Score (logrank) test = 13.72  on 2 df,   p=0.001
```



```
> ci.exp(c0)
     exp(Est.)      2.5%     97.5%
sexW 0.5880028 0.4237178 0.8159848
> ci.exp(c1)
     exp(Est.)      2.5%     97.5%
sexW  0.598566 0.4310936 0.8310985
age   1.017191 0.9989686 1.0357467
```

What do these estimates mean?

$$\lambda(t, x) = \lambda_0(t)\exp(\beta_1 x_1 + \beta_2 x_2)$$

Where is β_1 ? Where is β_2 ? Where is $\lambda_0(t)$?

What is the mortality RR for a 10 year age difference?

If mortality is assumed constant ($\lambda(t) = \lambda$), then the likelihood for the Cox-model is equivalent to a Poisson likelihood, which can be fitted using the `poisreg` family from the `Epi` package:

```
> ?poisreg

> p1 <- glm(cbind(status == 2, time) ~ sex + age,
+           family = poisreg,
+             data = lung)
> ci.exp(p1) # Poisson
             exp(Est.)       2.5%     97.5%
(Intercept) 0.03255152 0.01029228 0.1029511
sexW        0.61820515 0.44555636 0.8577537
age         1.01574132 0.99777446 1.0340317
> ci.exp(c1) # Cox
     exp(Est.)      2.5%     97.5%
sexW  0.598566 0.4310936 0.8310985
age   1.017191 0.9989686 1.0357467
```


Sex and age effects are quite close between the Poisson and the Cox models.

Poisson model has an intercept term, the estimate of the (assumed) constant underlying mortality.

The risk time part of the response (second argument in the `cbind`) was entered in units of months (remember we rescaled in the beginning?), the `(Intercept)` (taken from the `ci.exp`) is a rate per 1 person-month.

What age and sex does the `(Intercept)` refer to?

```
> ci.exp(p1) # Poisson
             exp(Est.)       2.5%     97.5%
(Intercept) 0.03255152 0.01029228 0.1029511
sexW        0.61820515 0.44555636 0.8577537
age         1.01574132 0.99777446 1.0340317
```


poisreg and poisson

`poisreg`: `cbind(d,y) ~ ...`

```
> p1 <- glm(cbind(status == 2, time) ~ sex + age,
+           family = poisreg,
+             data = lung)
```

`poisson`: `d ~ ...  + offset(log(y))`

```
> px <- glm(status == 2  ~ sex + age + offset(log(time)),
+           family = poisson,
+             data = lung)
> ## or:
> px <- glm(status == 2  ~ sex + age,
+           offset = log(time),
+           family = poisson,
+             data = lung)
```


Representation of follow-up: Lexis object

```
> L1 <- Lexis(exit = list(tfl = time),
+             exit.status = factor(status,
+                                  levels = 1:2,
+                                  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 tfl timescale.
> head(L1)
  tfl   lex.dur lex.Cst lex.Xst lex.id inst      time status age sex ph.ecog
1   0 10.053388   Alive    Dead      1    3 10.053388      2  74   M       1
2   0 14.948665   Alive    Dead      2    3 14.948665      2  68   M       0
3   0 33.182752   Alive   Alive      3    3 33.182752      1  56   M       0
4   0  6.899384   Alive    Dead      4    5  6.899384      2  57   M       1
5   0 29.010267   Alive    Dead      5    1 29.010267      2  60   M       0
6   0 33.577002   Alive   Alive      6   12 33.577002      1  74   M       1
  ph.karno pat.karno meal.cal wt.loss
1       90       100     1175      NA
2       90        90     1225      15
3       90        90       NA      15
4       90        60     1150      11
```


New variables in a Lexis object

`tfl`: time from lung cancer **at the time of entry**, therefore it is 0 for all persons; the entry time is 0 from the entry time. But it defines a **timescale**.

`lex.dur`: the **length** of time a person is in state `lex.Cst`, here measured in months, because `time` is.

`lex.Cst`: Current state, the state in which the `lex.dur` time is spent.

`lex.Xst`: eXit state, the state to which the person moves after the `lex.dur` time in `lex.Cst`.

`lex.id`: an id of each record in the source dataset. Can be explicitly set by `id=`.

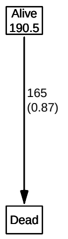
Lexis object: Overview of follow-up

Overkill?
The point is that the machinery generalizes to multistate data.

```
> summary(L1)
Transitions:
     To
From    Alive Dead  Records:  Events: Risk time:  Persons:
  Alive    63  165       228      165    2286.42       228
```

What is the average follow-up time for persons?

```
> boxes(L1, boxpos = TRUE, scale.Y = 12, digits.R = 2)
```



Explain the numbers in the graph.

Cox model using the Lexis-specific variables:

```
> cl <- coxph(Surv(tfl,
+                  tfl + lex.dur,
+                  lex.Xst == "Dead") ~ sex + age,
+             data = L1)
```

Surv(from-time, to-time, event indicator)

Using the Lexis features:

```
> cL <- coxph.Lexis(L1, tfl ~ sex + age)
survival::coxph analysis of Lexis object L1:
Rates for the transition Alive->Dead
Baseline timescale: tfl
> round(cbind(ci.exp(cL),
+             ci.exp(cl)), 3)
     exp(Est.)  2.5% 97.5% exp(Est.)  2.5% 97.5%
sexW     0.599 0.431 0.831     0.599 0.431 0.831
age      1.017 0.999 1.036     1.017 0.999 1.036
```


The crude Poisson model:

```
> pc <- glm(cbind(lex.Xst == "Dead", lex.dur) ~ sex + age,
+           family = poisreg,
+             data = L1)
```

or even simpler, by using the Lexis features:

```
> pL <- glm.Lexis(L1, ~ sex + age)
stats::glm Poisson analysis of Lexis object L1 with log link:
Rates for the transition: Alive->Dead
> round(cbind(ci.exp(pL),
+             ci.exp(pc)), 3)
            exp(Est.)  2.5% 97.5% exp(Est.)  2.5% 97.5%
(Intercept)     0.033 0.010 0.103     0.033 0.010 0.103
sexW            0.618 0.446 0.858     0.618 0.446 0.858
age             1.016 0.998 1.034     1.016 0.998 1.034
```


Poisson and Cox model

The crude Poisson model is a Cox-model with the (quite brutal) assumption that baseline rate is constant over time.

But results are similar:

```
> round(cbind(ci.exp(cL),
+             ci.exp(pL)[-1,]), 3)
     exp(Est.)  2.5% 97.5% exp(Est.)  2.5% 97.5%
sexW     0.599 0.431 0.831     0.618 0.446 0.858
age      1.017 0.999 1.036     1.016 0.998 1.034
```


Likelihood and records

Suppose a person is alive from t_e (entry) to t_x (exit) and that the person's status at t_x is d, where $d = 0$ means alive and $d = 1$ means dead. If we choose, say, two time points, t_1, t_2 between t_e and t_x, standard use of conditional probability (formally, repeated use of Bayes' formula) gives

$$\begin{aligned} \mathrm{P}\{d \text{ at } t_x \mid \text{entry at } t_e\} = & \mathrm{P}\{\text{survive } (t_e, t_1] \mid \text{alive at } t_e\} \times \\ & \mathrm{P}\{\text{survive } (t_1, t_2] \mid \text{alive at } t_1\} \times \\ & \mathrm{P}\{\text{survive } (t_2, t_3] \mid \text{alive at } t_2\} \times \\ & \mathrm{P}\{d \text{ at } t_x \mid \text{alive at } t_3\} \end{aligned}$$

Rates and likelihood

For a start assume that the mortality is constant over time $\lambda(t) = \lambda$:

$$\begin{aligned} \mathrm{P}\{\text{death during } (t, t+h]\} &\approx \lambda h \\ \Rightarrow \mathrm{P}\{\text{survive } (t, t+h]\} &\approx 1 - \lambda h \end{aligned} \qquad (1)$$

where the approximation gets better the smaller h is.

Dividing follow-up time

- Survival for a time span: $y = t_x - t_e$
- Subdivided in N intervals, each of length $h = y/N$
- Survival probability for the entire span from t_e to t_x is the **product** of probabilities of surviving each of the small intervals, conditional on being alive at the beginning each interval:

$$\mathrm{P}\{\text{survive } t_e \text{ to } t_x\} \approx (1 - \lambda h)^N = \left(1 - \frac{\lambda y}{N}\right)^N$$

Dividing follow-up time

- From mathematics it is known that $(1 + x/n)^n \to \exp(x)$ as $n \to \infty$ (some define $\exp(x)$ this way).
- So if we divide the time span y in small pieces we will have that $N \to \infty$:

$$\mathrm{P}\{\text{survive } t_e \text{ to } t_x\} \approx \left(1 - \frac{\lambda y}{N}\right)^N \to \exp(-\lambda y), \quad N \to \infty \qquad (2)$$

- The contribution to the likelihood from a person observed for a time span of length y is $\exp(-\lambda y)$, and the contribution to the log-likelihood is therefore $-\lambda y$.

Dividing follow-up time

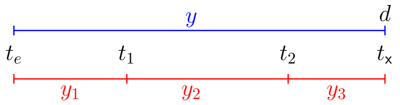
- A person dying at the end of the last interval, the contribution to the likelihood from the last interval will be
- the probability surviving till just before the end of the interval,
- **multiplied** by
- the probability of dying in the last tiny instant (of length ϵ) of the interval
- The probability of dying in this tiny instant is $\lambda\epsilon$
- log-likelihood contribution from this last instant is $\log(\lambda\epsilon) = \log(\lambda) + \log(\epsilon)$.

Total likelihood

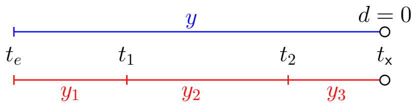
The total likelihood for one person is the product of all these terms from the follow-up intervals (i) for the person; and the log-likelihood (ℓ) is therefore:

$$\begin{aligned} \ell(\lambda) &= -\lambda \sum_i y_i + \sum_i d_i \log(\lambda) + \sum_i d_i \log(\epsilon) \\ &= \sum_i \left(d_i \log(\lambda) - \lambda y_i\right) + \sum_i d_i \log(\epsilon) \end{aligned}$$

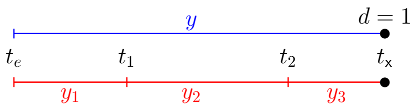
The last term does not depend on λ, so can be ignored



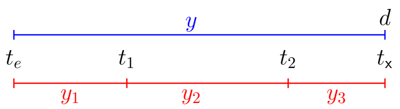
Probability	log-Likelihood
$\mathrm{P}(d \text{ at } t_x \mid \text{entry } t_e)$	$d\log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_e \to t_1 \mid \text{entry } t_e)$	$= 0\log(\lambda) - \lambda y_1$
$\times\, \mathrm{P}(\text{surv } t_1 \to t_2 \mid \text{entry } t_1)$	$+\, 0\log(\lambda) - \lambda y_2$
$\times\, \mathrm{P}(d \text{ at } t_x \mid \text{entry } t_2)$	$+\, d\log(\lambda) - \lambda y_3$



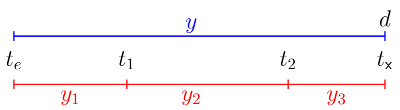
Probability	log-Likelihood
$\mathrm{P}(\text{surv } t_e \to t_x \mid \text{entry } t_e)$	$0\log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_e \to t_1 \mid \text{entry } t_e)$	$= 0\log(\lambda) - \lambda y_1$
$\times\, \mathrm{P}(\text{surv } t_1 \to t_2 \mid \text{entry } t_1)$	$+\, 0\log(\lambda) - \lambda y_2$
$\times\, \mathrm{P}(\text{surv } t_2 \to t_x \mid \text{entry } t_2)$	$+\, 0\log(\lambda) - \lambda y_3$



Probability	log-Likelihood
$\mathrm{P}(\text{event at } t_x \mid \text{entry } t_e)$	$1\log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_e \to t_1 \mid \text{entry } t_e)$	$= 0\log(\lambda) - \lambda y_1$
$\times\, \mathrm{P}(\text{surv } t_1 \to t_2 \mid \text{entry } t_1)$	$+\, 0\log(\lambda) - \lambda y_2$
$\times\, \mathrm{P}(\text{event at } t_x \mid \text{entry } t_2)$	$+\, 1\log(\lambda) - \lambda y_3$



Probability	log-Likelihood
$\mathrm{P}(d \text{ at } t_x \mid \text{entry } t_e)$	$d\log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_e \to t_1 \mid \text{entry } t_e)$	$= 0\log(\lambda) - \lambda y_1$
$\times\, \mathrm{P}(\text{surv } t_1 \to t_2 \mid \text{entry } t_1)$	$+\, 0\log(\lambda) - \lambda y_2$
$\times\, \mathrm{P}(d \text{ at } t_x \mid \text{entry } t_2)$	$+\, d\log(\lambda) - \lambda y_3$



Probability	log-Likelihood
$\mathrm{P}(d \text{ at } t_x \mid \text{entry } t_e)$	$d\log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_e \to t_1 \mid \text{entry } t_e)$	$= 0\log(\lambda_1) - \lambda_1 y_1$
$\times\, \mathrm{P}(\text{surv } t_1 \to t_2 \mid \text{entry } t_1)$	$+\, 0\log(\lambda_2) - \lambda_2 y_2$
$\times\, \mathrm{P}(d \text{ at } t_x \mid \text{entry } t_2)$	$+\, d\log(\lambda_3) - \lambda_3 y_3$

— allows different rates (λ_i) in each interval

Baseline hazard: splitting time

```
> S1 <- splitMulti(L1, tfl = 0:36)
> summary(L1)

Transitions:
     To
From    Alive Dead  Records:  Events: Risk time:  Persons:
  Alive    63  165       228      165    2286.42       228

> summary(S1)

Transitions:
     To
From    Alive Dead  Records:  Events: Risk time:  Persons:
  Alive  2234  165      2399      165    2286.42       228
```

What happended to no. records?

What happended to amount of risk time?

What happended to no. events?


```
> wh <- names(L1)[1:10] # names of variables in some order
> subset(L1, lex.id == 10)[,wh]

   tfl  lex.dur lex.Cst lex.Xst lex.id inst     time status age sex
10   0 5.453799   Alive    Dead     10    7 5.453799      2  61   M

> subset(S1, lex.id == 10)[,wh]

    tfl   lex.dur lex.Cst lex.Xst lex.id inst     time status age sex
163   0 1.0000000   Alive   Alive     10    7 5.453799      2  61   M
164   1 1.0000000   Alive   Alive     10    7 5.453799      2  61   M
165   2 1.0000000   Alive   Alive     10    7 5.453799      2  61   M
166   3 1.0000000   Alive   Alive     10    7 5.453799      2  61   M
167   4 1.0000000   Alive   Alive     10    7 5.453799      2  61   M
168   5 0.4537988   Alive    Dead     10    7 5.453799      2  61   M
```

In S1 each record now represents a small interval of follow-up for a person, so each person has many records.

Natural splines for baseline hazard

```
> ps <- glm(cbind(lex.Xst == "Dead", lex.dur)
+           ~ Ns(tfl, knots = seq(0, 36, 12)) + sex + age,
+           family = poisreg,
+             data = S1)
```

or even simpler:

```
> ps <- glm.Lexis(S1, ~ Ns(tfl, knots = seq(0, 36, 12)) + sex + age)

stats::glm Poisson analysis of Lexis object S1 with log link:
Rates for the transition: Alive->Dead

> ci.exp(ps)

                                 exp(Est.)        2.5%       97.5%
(Intercept)                      0.0189837 0.005700814  0.06321569
Ns(tfl, knots = seq(0, 36, 12))1 2.4038681 0.809442081  7.13896863
Ns(tfl, knots = seq(0, 36, 12))2 4.1500822 0.436273089 39.47798357
Ns(tfl, knots = seq(0, 36, 12))3 0.8398973 0.043928614 16.05849662
sexW                             0.5987171 0.431232662  0.83124998
age                              1.0165872 0.998377104  1.03512945
```


Comparing with estimates from the Cox-model and from the model with constant baseline:

```
> round(cbind(ci.exp(c1),
+             ci.exp(ps, subset = c("sex","age")),
+             ci.exp(pc, subset = c("sex","age"))), 3)

     exp(Est.)  2.5% 97.5% exp(Est.)  2.5% 97.5% exp(Est.)  2.5% 97.5%
sexW     0.599 0.431 0.831     0.599 0.431 0.831     0.618 0.446 0.858
age      1.017 0.999 1.036     1.017 0.998 1.035     1.016 0.998 1.034
```


But where is the baseline hazard?

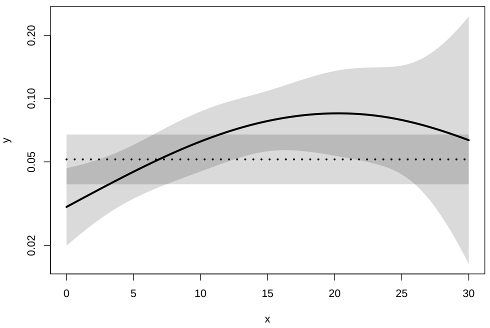
ps is a model for the hazard so we can predict the value of it at defined values for the covariates in the model:

```
> prf <- data.frame(tfl = seq(0, 30, 0.2),
+                   sex = "W",
+                   age = 60)
```

We can over-plot with the predicted rates from the model where mortality rates are constant, the only change is the model (pc instead of ps):

```
> matshade(prf$tfl, ci.pred(ps, prf),
+          plot = TRUE, log = "y", lwd = 3)
> matshade(prf$tfl, ci.pred(pc, prf), lty = 3, lwd = 3)
```

Here is the baseline hazard!



What are the units on the y-axis? Describe the mortality rates

Survival function and hazard function

$$S(t) = \exp(-\int_0^t \lambda(u)\,\mathrm{d}u)$$

Simple, but the CI for $S(t)$ not so simple. . .

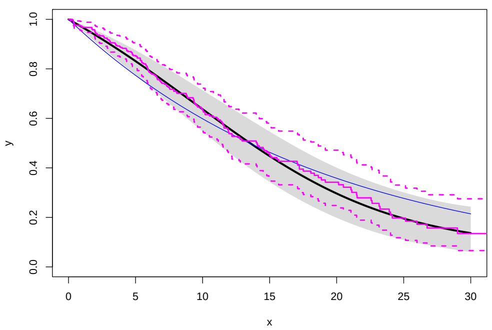
Implemented in the ci.surv function

Arguments: 1:model, 2:prediction data frame, 3:equidistance

Prediction data frame must correspond to a sequence of equidistant time points:

```
> matshade(prf$tfl, ci.surv(ps, prf, intl = 0.2),
+          plot = TRUE, ylim = 0:1, lwd = 3)
> lines(prf$tfl, ci.surv(pc, prf, intl = 0.2)[,1], col="blue")
> lines(survfit(c1, newdata = data.frame(sex = "W", age = 60)),
+       lwd = 2, lty = 1, col="magenta")
```

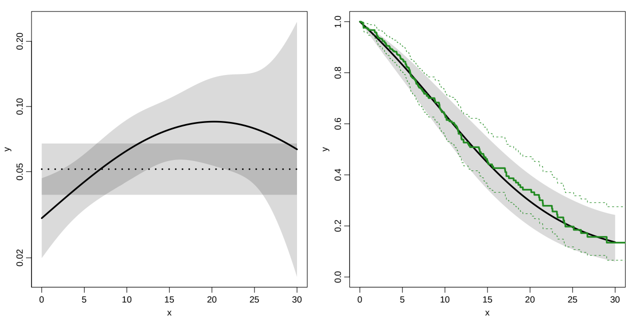

Survival functions



Hazard and survival functions

```
> par(mfrow = c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6)
> #
> # hazard scale
> matshade(prf$tfl, ci.pred(ps, prf),
+          plot = TRUE, log = "y", lwd = 3)
> matshade(prf$tfl, ci.pred(pc, prf), lty = 3, lwd = 3)
> #
> # survival
> matshade(prf$tfl, ci.surv(ps, prf, intl = 0.2),
+          plot = TRUE, ylim = 0:1, lwd = 3)
> lines(survfit(c1, newdata = data.frame(sex = "W", age = 60)),
+       col = "forestgreen", lwd = 3, conf.int = FALSE)
> lines(survfit(c1, newdata = data.frame(sex = "W", age = 60)),
+       col = "forestgreen", lwd = 1, lty = 1)
```


Hazard and survival functions

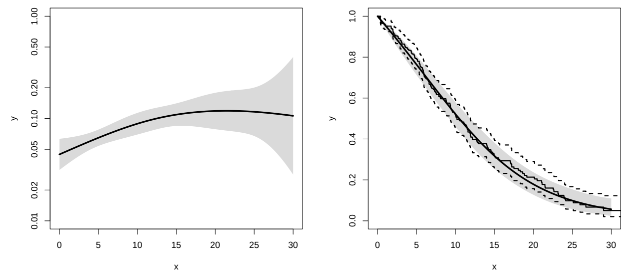


K-M estimator and smooth Poisson model

Kaplan-Meier estimator and compared to survival from corresponding Poisson-model, which is one with time (tfl) as the only covariate:

```
> par(mfrow=c(1,2))
> pk <- glm(cbind(lex.Xst == "Dead",
+                 lex.dur) ~ Ns(tfl, knots = seq(0, 36, 12)),
+           family = poisreg,
+             data = S1)
> # hazard
> matshade(prf$tfl, ci.pred(pk, prf),
+          plot = TRUE, log = "y", lwd = 3, ylim = c(0.01,1))
> # survival from smooth model
> matshade(prf$tfl, ci.surv(pk, prf, intl = 0.2) ,
+          plot = TRUE, lwd = 3, ylim = 0:1)
> # K-M estimator
> lines(km, lwd = 2)
```


K-M estimator and smooth Poisson model

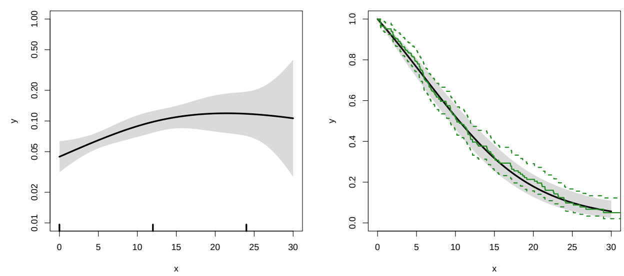


K-M estimator and smooth Poisson model

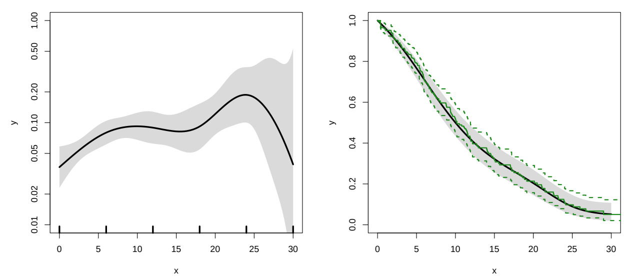
We can explore how the tightness of the knots in the smooth model influence the underlying hazard and the resulting survival function:

```
> zz <- function(dk) # distance between knots
+ {
+ par(mfrow=c(1,2))
+ kn <- seq(0, 36, dk)
+ pk <- glm(cbind(lex.Xst == "Dead",
+                 lex.dur) ~ Ns(tfl, knots = kn),
+           family = poisreg,
+             data = S1)
+ matshade(prf$tfl, ci.pred(pk, prf),
+          plot = TRUE, log = "y", lwd = 3, ylim = c(0.01,1))
+ rug(kn, lwd=3)
+
+ matshade(prf$tfl, ci.surv(pk, prf, intl = 0.2) ,
+          plot = TRUE, lwd = 3, ylim = 0:1)
+ lines(km, lwd = 2, col = "forestgreen")
+ }
> zz(12)
```

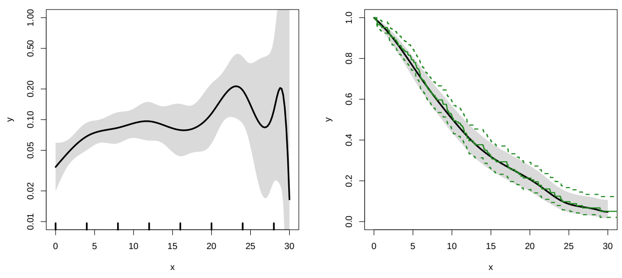

K-M estimator and smooth Poisson model



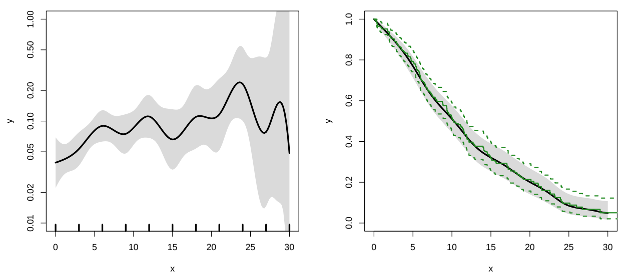
K-M estimator and smooth Poisson model



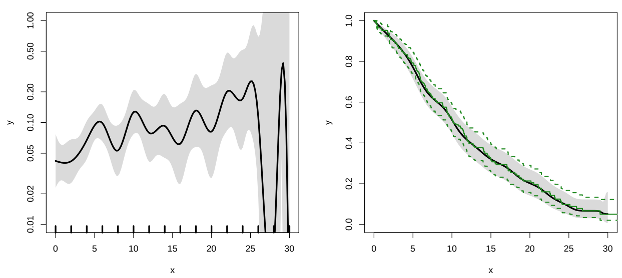
K-M estimator and smooth Poisson model



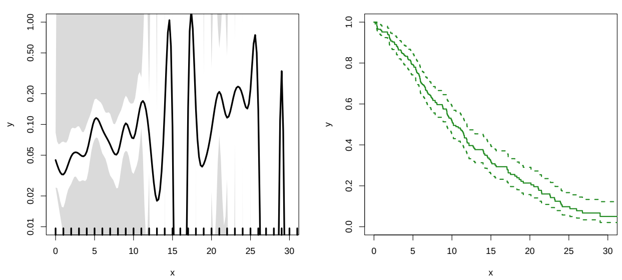
K-M estimator and smooth Poisson model



K-M estimator and smooth Poisson model



K-M estimator and smooth Poisson model



Survival analysis summary

- 1 to 1 correspondence between hazard function and survival function
- K-M and Cox use a very detailed baseline hazard (omits it)
- Smooth parametric hazard function more credible:
  - Define Lexis object
  - Split along time
  - Fit Poisson model
  - Prediction data frame
  - ci.pred to get baseline rates
  - ci.surv to get baseline survival


```
> data(lung)
> lung$sex <- factor(lung$sex, labels=c("M", "F"))
> Lx <- Lexis(exit = list(tfe=time),
+       exit.status = factor(status,labels = c("Alive", "Dead")),
+              data = lung)
> sL <- splitMulti(Lx, tfe=seq(0, 1200, 10))
```

Smooth parametric hazard function

```
> m0 <- glm.Lexis(sL, ~ Ns(tfe, knots = seq(0, 1000, 200)) + sex + age)
```

Prediction data frame

```
> nd <- data.frame(tfe = seq(0, 900, 20) + 10, sex = "M", age = 65)
```

Predictions

```
> rate <- ci.pred(m0, nd) * 365.25 # per year, not per day
> surv <- ci.surv(m0, nd, int = 20)
```

Plot the rates

```
> matshade(nd$tfe, rate, log = "y", plot = TRUE)
```

Plot the survival function

```
> matshade(nd$tfe - 10, surv, ylim = c(0, 1), plot = TRUE)
```



```
> library(survival)
> library(Epi)
> library(popEpi)
> # popEpi::splitMulti returns a data.frame rather than a data.table
> options("popEpi.datatable" = FALSE)
> library(tidyverse)
> clear()

> data(DMlate)
> # str(DMlate)
> set.seed(1952)
> DMlate <- DMlate[sample(1:nrow(DMlate), 2000),]
> str(DMlate)
'data.frame':        2000 obs. of  7 variables:
 $ sex  : Factor w/ 2 levels "M","F": 2 1 2 1 1 1 1 1 1 1 ...
 $ dobth: num  1964 1944 1957 1952 1952 ...
 $ dodm : num  2003 2006 2008 2007 2003 ...
 $ dodth: num  NA NA NA NA NA NA NA NA NA NA ...
 $ dooad: num  NA 2006 NA 2007 2006 ...
 $ doins: num  NA NA NA 2008 NA ...
 $ dox  : num  2010 2010 2010 2010 2010 ...
> head(DMlate)
```


Lexis object from DM to Death

```
> Ldm <- Lexis(entry = list(per = dodm,
+                           age = dodm - dobth,
+                           tfd = 0),
+               exit = list(per = dox),
+        exit.status = factor(!is.na(dodth),
+                            labels = c("DM","Dead")),
+               data = DMlate)
NOTE: entry.status has been set to "DM" for all.
NOTE: Dropping  1  rows with duration of follow up < tol
> summary(Ldm)
Transitions:
     To
From    DM Dead  Records:  Events: Risk time:  Persons:
  DM 1521  478      1999      478   10742.34      1999
```


Cut follow-up at the date of OAD

```
> Cdm <- cutLexis(Ldm,
+                 cut = Ldm$dooad,
+           timescale = "per",
+           new.state = "OAD")
> summary(Cdm)
Transitions:
     To
From    DM  OAD Dead  Records:  Events: Risk time:  Persons:
  DM   685  634  226      1545      860     5414.3      1545
  OAD    0  836  252      1088      252     5328.1      1088
  Sum  685 1470  478      2633     1112    10742.3      1999
```

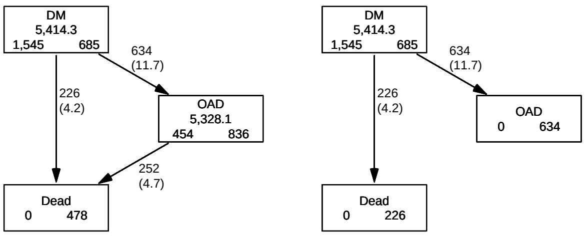

Cut follow-up at the date of OAD, dooad

```
> subset(Ldm, lex.id %in% c(2:3,20))[,c(1:7,12)]
          per    age tfd lex.dur lex.Cst lex.Xst lex.id  dooad
235221 2005.6 61.517   0  4.3532      DM      DM      2 2005.8
230872 2007.9 51.097   0  2.1109      DM      DM      3     NA
114618 2006.0 73.183   0  3.7919      DM    Dead     20 2007.0
> subset(Cdm, lex.id %in% c(2:3,20))[,c(1:7,12)]
        per    age     tfd lex.dur lex.Cst lex.Xst lex.id  dooad
2    2005.6 61.517 0.00000 0.13415      DM     OAD      2 2005.8
2001 2005.8 61.651 0.13415 4.21903     OAD     OAD      2 2005.8
3    2007.9 51.097 0.00000 2.11088      DM      DM      3     NA
20   2006.0 73.183 0.00000 1.01848      DM     OAD     20 2007.0
2019 2007.0 74.201 1.01848 2.77344     OAD    Dead     20 2007.0
```

Restrict to those alive in DM

```
> Adm <- subset(Cdm, lex.Cst == "DM")
> summary(Adm)
Transitions:
     To
From  DM OAD Dead  Records:  Events: Risk time:  Persons:
  DM 685 634  226      1545      860     5414.3      1545
> par(mfrow=c(1,2))
> boxes(Cdm, boxpos = TRUE, scale.R = 100, show.BE = TRUE)
> boxes(Adm, boxpos = TRUE, scale.R = 100, show.BE = TRUE)
```


Transitions in Cdm and Adm



Survival function?

$$S(t) = \exp\left(-\int_0^t \lambda(u) + \mu(u)\,\mathrm{d}u\right)$$
$$S(t) = \exp\left(-\int_0^t \lambda(u)\,\mathrm{d}u\right)$$
$$S(t) = \exp\left(-\int_0^t \mu(u)\,\mathrm{d}u\right)$$

Survival function?

- Regarding either Dead or OAD as censorings — or neither?
- **Simple survival**: what is the probability of being in each of the states Alive and Dead
  —depends on **one** rate, Alive → Dead
- **Competing risks**: what is the probability of being in each of the states DM, OAD and Dead
  —depends on **two** rates, DM → OAD and DM → Dead

Survival function and Cumulative risk function

survfit does the trick; the requirements are:

1. (start, stop, event) arguments to Surv
2. the third argument to the Surv function is a factor
3. an id argument is given, pointing to an id variable that links together records belonging to the same person.
4. the initial state (DM) must be the first level of the factor lex.Xst

Survival function and Cumulative risk function

```
> levels(Adm$lex.Xst)
[1] "DM"   "OAD"  "Dead"
> m3 <- survfit(Surv(tfd, tfd + lex.dur, lex.Xst) ~ 1,
+                 id = lex.id,
+               data = Adm)
> # names(m3)
> m3$states
[1] "(s0)" "OAD"  "Dead"
> head(cbind(time = m3$time, m3$pstate))
          time
[1,] 0.0027379 0.99871 0.0012945 0.00000000
[2,] 0.0054757 0.99288 0.0064725 0.00064725
[3,] 0.0082136 0.98900 0.0090615 0.00194175
[4,] 0.0109514 0.98770 0.0097087 0.00258900
[5,] 0.0136893 0.98382 0.0135922 0.00258900
[6,] 0.0164271 0.98058 0.0168285 0.00258900
```

—this is called the Aalen-Johansen estimator of state probabilities

Survival function and cumulative risks—formulae

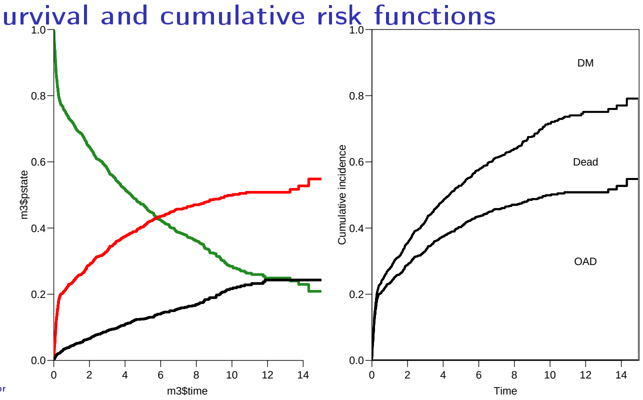
$$S(t) = \exp\Big(-\int_0^t \lambda(u) + \mu(u)\,\mathrm{d}u\Big)$$
$$R_{\texttt{Dead}}(t) = \int_0^t \mu(u) S(u)\,\mathrm{d}u$$
$$R_{\texttt{OAD}}(t) = \int_0^t \lambda(u) S(u)\,\mathrm{d}u)$$
$$= \int_0^t \lambda(u) \exp\Big(-\int_0^u \lambda(s) + \mu(s)\,\mathrm{d}s\Big)\,\mathrm{d}u$$

$$S(t) + R_{\texttt{OAD}}(t) + R_{\texttt{Dead}}(t) = 1, \quad \forall t$$

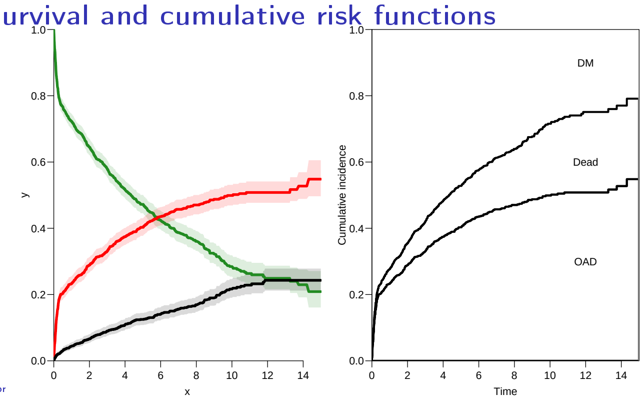
Survival function and cumulative risks

```
> par( mfrow=c(1,2) )
> matplot(m3$time, m3$pstate,
+         type="s", lty=1, lwd=4,
+         col=c("ForestGreen","red","black"),
+         xlim=c(0,15), xaxs="i",
+         ylim=c(0,1), yaxs="i" )
> stackedCIF(m3, lwd=3, xlim=c(0,15), xaxs="i", yaxs="i" )
> text(rep(12,3), c(0.9,0.3,0.6), levels(Cdm))
> box(bty="o")
> par( mfrow = c(1,2) )
> matshade(m3$time, cbind(m3$pstate,
+                         m3$lower,
+                         m3$upper)[,c(1,4,7,2,5,8,3,6,9)],
+          plot = TRUE, lty = 1, lwd = 4,
+          col = c("ForestGreen","red","black"),
+          xlim=c(0,15), xaxs="i",
+          ylim = c(0,1), yaxs = "i")
> stackedCIF(m3, lwd=3, xlim=c(0,15), xaxs="i", yaxs="i" )
> text(rep(12,3), c(0.9,0.3,0.6), levels(Cdm))
> box(bty="o")
```


Survival and cumulative risk functions



Survival and cumulative risk functions



Survival function and cumulative risks—don't

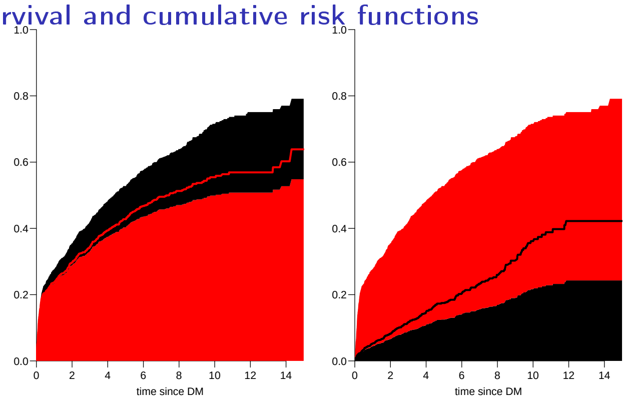
$$
\begin{aligned}
S(t) &= \exp\Big(-\int_0^t \lambda(u) + \mu(u)\,\mathrm{d}u\Big) \\
R_{\texttt{Dead}}(t) &= \int_0^t \mu(u) S(u)\,\mathrm{d}u \\
R_{\texttt{OAD}}(t) &= \int_0^t \lambda(u) S(u)\,\mathrm{d}u) \\
&= \int_0^t \lambda(u) \exp\Big(-\int_0^u \lambda(s) + \mu(s)\,\mathrm{d}s\Big)\,\mathrm{d}u \\
&\neq \int_0^t \lambda(u) \exp\Big(-\int_0^u \lambda(s)\,\mathrm{d}s\Big)\,\mathrm{d}u \\
&= 1 - \exp\Big(-\int_0^t \lambda(s)\,\mathrm{d}s\Big) \text{ — nice formula, but wrong!}
\end{aligned}
$$

Probability of `OAD` **assuming** `Dead` does not exist **and** rate of `OAD` unchanged!

Survival function and cumulative risks—don't

```
> m2 <- survfit(Surv(tfd,
+                    tfd + lex.dur,
+                    lex.Xst == "OAD" ) ~ 1,
+               data = Adm)
> M2 <- survfit(Surv(tfd,
+                    tfd + lex.dur,
+                    lex.Xst == "Dead") ~ 1,
+               data = Adm)
> par(mfrow = c(1,2))
> mat2pol(m3$pstate, c(2,3,1), x = m3$time,
+         col = c("red", "black", "transparent"),
+         xlim=c(0,15), xaxs="i",
+         yaxs = "i", xlab = "time since DM", ylab = "" )
>   lines(m2$time, 1 - m2$surv, lwd = 3, col = "red" )
> mat2pol(m3$pstate, c(3,2,1), x = m3$time, yaxs = "i",
+         col = c("black","red","transparent"),
+         xlim=c(0,15), xaxs="i",
+         yaxs = "i", xlab = "time since DM", ylab = "" )
>   lines(M2$time, 1 - M2$surv, lwd = 3, col = "black" )
```


Survival and cumulative risk functions



Cause-specific rates

- There is nothing wrong with modeling the cause-specific event-rates, the problem lies in how you transform them into probabilities.
- The relevant model for a competing risks situation normally consists of separate models for each of the cause-specific rates.
- ...not for technical or statistical reasons, but for **substantial** reasons:
  it is unlikely that rates of different types of event (OAD initiation and death, say) depend on time in the same way.

Cause-specific rates

```
> Sdm <- splitMulti(Adm, tfd = seq(0, 20, 0.1))
> summary(Adm)

Transitions:
     To
From  DM OAD Dead  Records:  Events: Risk time:  Persons:
  DM 685 634  226      1545      860     5414.3      1545

> summary(Sdm)

Transitions:
     To
From    DM OAD Dead  Records:  Events: Risk time:  Persons:
  DM 54064 634  226     54924      860     5414.3      1545
```

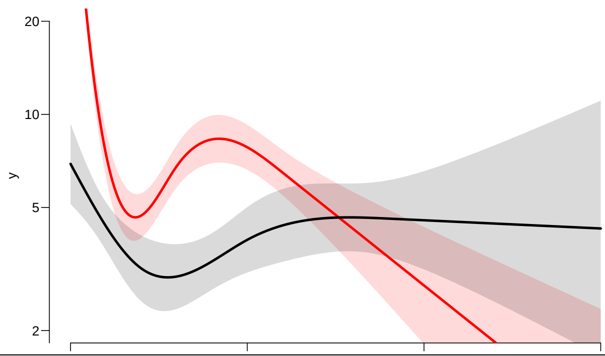

Cause-specific rates

```
> round(cbind(
+ with(subset(Sdm, lex.Xst == "OAD" ), quantile(tfd + lex.dur, 0:5/5)),
+ with(subset(Sdm, lex.Xst == "Dead"), quantile(tfd + lex.dur, 0:5/5))), 2)

      [,1]  [,2]
0%    0.00  0.01
20%   0.09  0.51
40%   0.24  1.73
60%   1.27  3.58
80%   3.37  6.20
100% 14.31 11.86

> okn <- c(0, 0.5, 3, 10)
> dkn <- c(0, 2.0, 5,  9)
>  OAD.glm <- glm.Lexis(Sdm, ~ Ns(tfd, knots = okn), to = "OAD" )

stats::glm Poisson analysis of Lexis object Sdm with log link:
Rates for the transition: DM->OAD

> Dead.glm <- glm.Lexis(Sdm, ~ Ns(tfd, knots = dkn), to = "Dead")

stats::glm Poisson analysis of Lexis object Sdm with log link:
Rates for the transition: DM->Dead
```

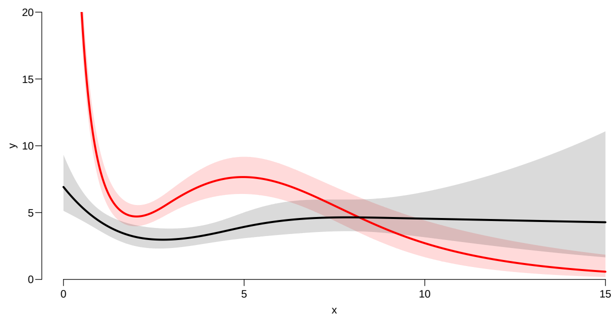

Cause-specific rates

```
> int <- 0.01
> nd <- data.frame(tfd = seq(0, 15, int))
> l.glm <- ci.pred( OAD.glm, nd)
> m.glm <- ci.pred(Dead.glm, nd)
> matshade(nd$tfd,
+          cbind(l.glm, m.glm) * 100,
+          plot = TRUE,
+          yaxs="i", ylim = c(0, 20),
+        # log = "y", ylim = c(2, 20),
+          col = rep(c("red","black"), 2), lwd = 3)
```


Survival and cumulative risk functions



Survival and cumulative risk functions



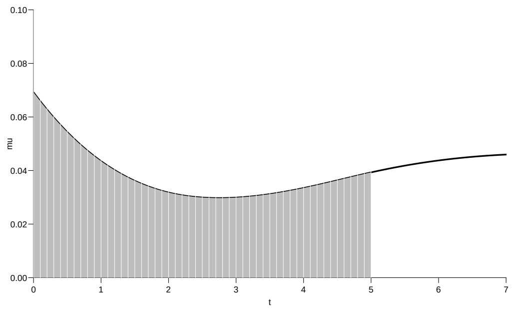
Integrals with R

- Integrals look scary to many people, but they are really just areas under curves.
- The key is to understand how a curve is represented in R.
- A curve of the function $\mu(t)$ is a set of two vectors:
  one vector of ts and one vector $y = \mu(t)$s.
- When we have a model such as the `glm` above that estimates the mortality as a function of time (`tfd`), we can get the mortality as a funtion of time by first choosing the timepoints, say from 0 to 15 years in steps of 0.01 year ($\approx$ 4 days), using `ci.pred`
- Then use the formuale with all the integrals to get the state probabilities.

Integrals with R

```
> t <- seq(0, 15, 0.01)
> nd <- data.frame(tfd = t)
> mu <- ci.pred(Dead.glm, nd)[,1]
> head(cbind(t, mu))
     t        mu
1 0.00 0.069190
2 0.01 0.068853
3 0.02 0.068517
4 0.03 0.068183
5 0.04 0.067851
6 0.05 0.067520
> plot(t, mu, type="l", lwd = 3,
+      xlim = c(0, 7), xaxs = "i",
+      ylim = c(0, 0.1), yaxs = "i")
> polygon(t[c(1:501,501:1)], c(mu[1:501], rep(0, 501)),
+         col = "gray", border = "transparent")
> abline(v=0:50/10, col="white")
```


Integrals with R



Numerical integration with R

```
> mid <- function(x) x[-1] - diff(x) / 2
> (x <- c(1:5, 7, 10))
[1]  1  2  3  4  5  7 10
> mid(x)
[1] 1.5 2.5 3.5 4.5 6.0 8.5
```

`mid(x)` is a vector that is 1 shorter than the vector `x`, just as `diff(x)` is.

So if we want the integral over the period 0 to 5 years, we want the sum over the first 500 intervals, corresponding to the first 501 interval endpoints:

```
> cbind(diff(t), mid(mu))[1:5,]
  [,1]     [,2]
2 0.01 0.069022
3 0.01 0.068685
4 0.01 0.068350
5 0.01 0.068017
6 0.01 0.067686
```


Numerical integration with R

In practice we will want the integral **function** of μ, so for every t we want $M(t) = \int_0^t \mu(s)\,\mathrm{d}(s)$. This is easily accomplished by the function `cumsum`:

```
> Mu <- c(0, cumsum(diff(t) * mid(mu)))
> head(cbind(t, Mu))
     t         Mu
  0.00 0.00000000
2 0.01 0.00069022
3 0.02 0.00137707
4 0.03 0.00206057
5 0.04 0.00274074
6 0.05 0.00341760
```

Note the first value which is the integral from 0 to 0, so by definition 0.

Cumulative risks from parametric models

If we have estimates of λ and μ as functions of time, we can derive the cumulative risks.

In practice this will be by numerical integration; compute the rates at closely spaced intervals and evaluate the integrals as sums. This is easy.

but what is not so easy is to come up with confidence intervals for the cumulative risks.

Simulation of cumulative risks: `ci.Crisk`

1. generate a random vector from the multivariate normal distribution with mean equal to the parameters of the model, and variance-covariance equal to the estimated variance-covariance of the parameter estimates
2. use this to generate a simulated set of rates $(\lambda(t), \mu(t))$, evaluated a closely spaced times
3. use these in numerical integration to derive state probabilities at these times
4. repeat 1000 times, say, to obtain 1000 sets of state probabilities at these times
5. use these to derive confidence intervals for the state probabilities as the 2.5 and 97.5 percentiles of the state probabilities at each time

Cumulative risks from parametric models

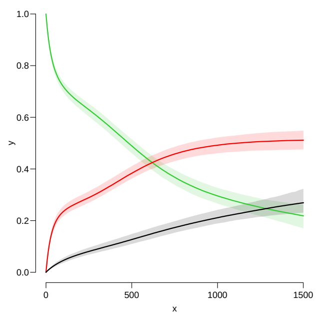
```
> cR <- ci.Crisk(mods = list(OAD =  OAD.glm,
+                            Dead = Dead.glm),
+                  nd = nd)
Times are assumed to be in the column tfd at equal distances of 0.01
> str(cR)
List of 3
 $ Crisk: num [1:1502, 1:3, 1:3] 1 0.992 0.984 0.976 0.969 ...
  ..- attr(*, "dimnames")=List of 3
  .. ..$ time : chr [1:1502] "0" "1" "2" "3" ...
  .. ..$ cause: chr [1:3] "Surv" "OAD" "Dead"
  .. ..$      : chr [1:3] "50%" "2.5%" "97.5%"
 $ Srisk: num [1:1502, 1:2, 1:3] 0 0.000694 0.001378 0.002054 0.002721 ...
  ..- attr(*, "dimnames")=List of 3
  .. ..$ time : chr [1:1502] "0" "1" "2" "3" ...
  .. ..$ cause: chr [1:2] "Dead" "Dead+OAD"
  .. ..$      : chr [1:3] "50%" "2.5%" "97.5%"
 $ Stime: num [1:1501, 1:3, 1:3] 0.00996 0.01984 0.02964 0.03936 0.04901 ...
  ..- attr(*, "dimnames")=List of 3
  .. ..$      : chr [1:1501] "1" "2" "3" "4" ...
  .. ..$ cause: chr [1:3] "Surv" "OAD" "Dead"
```


Cumulative risks from parametric models

So now plot the cumulative *risks* of being in each of the states (the `Crisk` component):

```
> matshade(as.numeric(dimnames(cR$Crisk)[[1]]),
+          cbind(cR$Crisk[,1,],
+                cR$Crisk[,2,],
+                cR$Crisk[,3,]), plot = TRUE,
+          lwd = 2, col = c("limegreen","red","black"))
```


Survival and cumulative risk functions



Stacked probabilities: (`matrix` 2 `polygons`)

```
> mat2pol(cR$Crisk[,3:1,1], col = c("forestgreen","red","black")[3:1])
```

1st argument to `mat2pol` must be a 2-dimensional matrix, with rows representing the x-axis of the plot, and columns states.

The component `Srisk` has the confidence limits of the stacked probabilities:

```
> mat2pol(cR$Crisk[,3:1,1], col = c("forestgreen","red","black")[3:1])
> matlines(as.numeric(dimnames(cR$Srisk)[["time"]]),
+          cbind(cR$Srisk[,"Dead"    ,2:3],
+                cR$Srisk[,"Dead+OAD",2:3]),
+          lty = "32", lwd = 2, col = gray(0.7))
```

Survival and cumulative risk functions

1| handout:0>../graph/cmpr-srisk 2|
handout:1>../graph/cmpr-sriskci

Expected life time: using simulated objects

The areas between the lines (up to say 10 years) are **expected sojourn times**, that is:

- expected years alive without OAD
- expected years lost to death without OAD
- expected years after OAD, including years dead after OAD

Not all of these are of direct relevance; actually only the first may be so.

They are available (with simulation-based confidence intervals) in the component of `cR`, `Stime` (`S`ojourn `time`).

Expected life time: using simulated objects

A relevant quantity would be the expected time alive without OAD during the first 5, 10 and 15 years:

```
> str(cR$Stime)
 num [1:1501, 1:3, 1:3] 0.00996 0.01984 0.02964 0.03936 0.04901 ...
 - attr(*, "dimnames")=List of 3
  ..$      : chr [1:1501] "1" "2" "3" "4" ...
  ..$ cause: chr [1:3] "Surv" "OAD" "Dead"
  ..$      : chr [1:3] "50%" "2.5%" "97.5%"
> round(cR$Stime[c("5","10","15"),"Surv",], 1)
    50% 2.5% 97.5%
 5  0.0  0.0   0.0
 10 0.1  0.1   0.1
 15 0.1  0.1   0.1
```


BAckground: Steno 2 trial

- Clinical trisl for diabetes ptt. with kidney disease (micro-albuminuria)
- 80 ptt. randomised to either of
  - Conventional treatment
  - Intensified multifactorial treament
- 1993–2001
- follow-up till 2018

Steno 2 trial: goal

- Is there a treatment effect on:
  - CVD mortality
  - non-CVD mortality
  - Albuminuria state
- Rate-ratios
- Life times
- Changes in clinical parameters


```
> data(steno2)
> steno2 <- cal.yr(steno2)
> steno2 <- transform(steno2,
+                     doEnd = pmin(doDth, doEnd, na.rm = TRUE))
> str(steno2)
'data.frame':        160 obs. of  14 variables:
 $ id      : num  1 2 3 4 5 6 7 8 9 10 ...
 $ allo    : Factor w/ 2 levels "Int","Conv": 1 1 2 2 2 2 2 1 1 1 ...
 $ sex     : Factor w/ 2 levels "F","M": 2 2 2 2 2 2 1 2 2 2 ...
 $ baseCVD : num  0 0 0 0 0 1 0 0 0 0 ...
 $ deathCVD: num  0 0 0 0 1 0 0 0 1 0 ...
 $ doBth   : 'cal.yr' num  1932 1947 1943 1945 1936 ...
 $ doDM    : 'cal.yr' num  1991 1982 1983 1977 1986 ...
 $ doBase  : 'cal.yr' num  1993 1993 1993 1993 1993 ...
 $ doCVD1  : 'cal.yr' num  2014 2009 2002 1995 1994 ...
 $ doCVD2  : 'cal.yr' num  NA 2009 NA 1997 1995 ...
 $ doCVD3  : 'cal.yr' num  NA 2010 NA 2003 1998 ...
 $ doESRD  : 'cal.yr' num  NaN NaN NaN NaN 1998 ...
 $ doEnd   : 'cal.yr' num  2015 2015 2002 2003 1998 ...
 $ doDth   : 'cal.yr' num  NA NA 2002 2003 1998 ...
```


A `Lexis` object

```
> L2 <- Lexis(entry = list(per = doBase,
+                          age = doBase - doBth,
+                          tfi = 0),
+             exit = list(per = doEnd),
+      exit.status = factor(deathCVD + !is.na(doDth),
+                           labels=c("Mic","D(oth)","D(CVD)")),
+               id = id,
+             data = steno2)
NOTE: entry.status has been set to "Mic" for all.
```

Explain the coding of `exit.status`.

A `Lexis` object

```
> summary(L2, t = TRUE)
Transitions:
     To
From  Mic D(oth) D(CVD)  Records:  Events: Risk time:  Persons:
  Mic  67     55     38       160       93    2416.59       160

Timescales:
per age tfi
 ""  ""  ""
```

How many persons are there in the cohort?

How many deaths are there in the cohort?

How much follow-up time is there in the cohort?

How many states are there in the model (so far)?

Albuminuria status

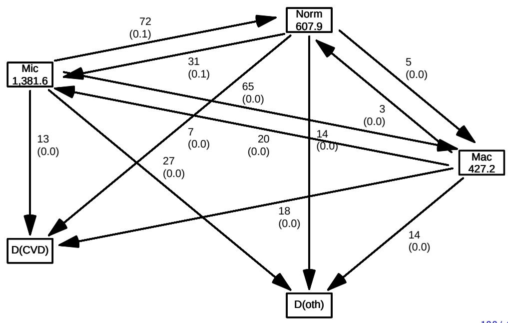
```
> data(st2alb) ; head(st2alb, 3)
  id       doTr state
1  1 1993-06-12   Mic
2  1 1995-05-13  Norm
3  1 2000-01-26   Mic
> cut2 <- rename(cal.yr(st2alb),
+                lex.id = id,
+                   cut = doTr,
+             new.state = state)
> with(cut2, addmargins(table(table(lex.id))))

 1   2   3   4   5 Sum
 4  25  40  46  41 156
```

What does this table mean?

Albuminuria status as states

```
> L3 <- rcutLexis(L2, cut2, time = "per")
> summary(L3)
Transitions:
     To
From   Mic Norm Mac D(oth) D(CVD)  Records:  Events: Risk time:  Persons:
  Mic  299   72  65     27     13       476      177    1381.57       160
  Norm  31   90   5     14      7       147       57     607.86        69
  Mac   20    3  44     14     18        99       55     427.16        64
  Sum  350  165 114     55     38       722      289    2416.59       160
> boxes(L3, boxpos = TRUE, cex = 0.8)
```

What's wrong with this



What's in jump

```
> (jump <-
+ subset(L3, (lex.Cst == "Norm" & lex.Xst == "Mac") |
+             (lex.Xst == "Norm" & lex.Cst == "Mac"))[,
+        c("lex.id", "per", "lex.dur","lex.Cst", "lex.Xst")])
    lex.id      per    lex.dur lex.Cst lex.Xst
291     70 1999.487  2.6748802     Mac    Norm
353     86 2001.759 12.8158795    Norm     Mac
506    130 2000.910  1.8781656     Mac    Norm
511    131 1997.756  4.2354552    Norm     Mac
525    136 1997.214  0.4709103     Mac    Norm
526    136 1997.685  4.2436687    Norm     Mac
654    171 1996.390  5.3388090    Norm     Mac
676    175 2004.585  9.8836413    Norm     Mac
```

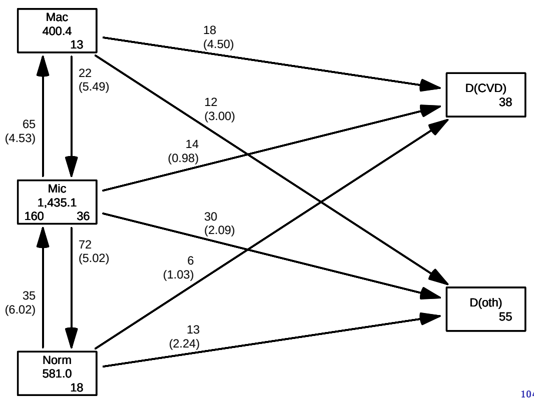
—and what will you do about it?

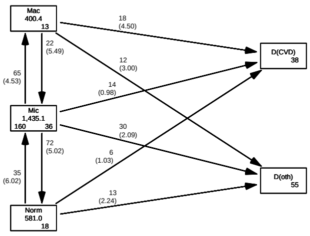
How to fix things

```
> set.seed(1952)
> xcut <- transform(jump,
+                   cut = per + lex.dur * runif(per, 0.1, 0.9),
+             new.state = "Mic")
> xcut <- select(xcut, c(lex.id, cut, new.state))
> L4 <- rcutLexis(L3, xcut)
> L4 <- Relevel(L4, c("Norm","Mic","Mac","D(CVD)","D(oth)"))
> summary(L4)

Transitions:
     To
From   Norm Mic Mac D(CVD) D(oth)  Records:  Events: Risk time:  Persons:
  Norm   90  35   0      6     13       144       54     581.04        66
  Mic    72 312  65     14     30       493      181    1435.14       160
  Mac     0  22  41     18     12        93       52     400.41        60
  Sum   162 369 106     38     55       730      287    2416.59       160
```


Plot the boxes

```
> boxes(L4, boxpos = list(x = c(20, 20, 20, 80, 80),
+                         y = c(10, 50, 90, 75, 25)),
+          show.BE = "nz",
+          scale.R = 100, digits.R = 2,
+          cex = 0.9, pos.arr = 0.3)
```



Explain all the numbers in the graph.

Describe the overall effect of albuminuria on the two mortality rates.

Modeling transition rates

- A model with a smooth effect of timescales on the rates require follow-up in small bits
- Achieved by splitLexis (or splitMulti from popEpi)
- Compare the Lexis objects


```
> S4 <- splitMulti(L4, tfi = seq(0, 25, 1/2))
> summary(L4)

Transitions:
     To
From   Norm Mic Mac D(CVD) D(oth)  Records:  Events: Risk time:  Persons:
  Norm   90  35   0      6     13       144       54     581.04        66
  Mic    72 312  65     14     30       493      181    1435.14       160
  Mac     0  22  41     18     12        93       52     400.41        60
  Sum   162 369 106     38     55       730      287    2416.59       160

> summary(S4)

Transitions:
     To
From   Norm  Mic Mac D(CVD) D(oth)  Records:  Events: Risk time:  Persons:
  Norm 1252   35   0      6     13      1306       54     581.04        66
  Mic    72 3101  65     14     30      3282      181    1435.14       160
  Mac     0   22 844     18     12       896       52     400.41        60
  Sum  1324 3158 909     38     55      5484      287    2416.59       160
```

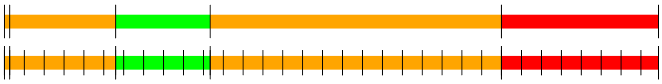

How the split works:

```
> subset(L4, lex.id == 96)[,1:7]
         per      age       tfi   lex.dur lex.Cst lex.Xst lex.id
417 1993.650 51.53183 0.0000000 0.4544832     Mic    Norm     96
418 1994.104 51.98631 0.4544832 2.5790554    Norm    Norm     96
419 1996.683 54.56537 3.0335387 1.9028063    Norm    Norm     96
420 1998.586 56.46817 4.9363450 2.8966461    Norm  D(CVD)     96
> subset(S4, lex.id == 96)[c(1:5,NA,33:35),1:7]
     lex.id      per      age       tfi    lex.dur lex.Cst lex.Xst
3138     96 1993.650 51.53183 0.0000000 0.45448323     Mic    Norm
3139     96 1994.104 51.98631 0.4544832 0.04551677    Norm    Norm
3140     96 1994.150 52.03183 0.5000000 0.50000000    Norm    Norm
3141     96 1994.650 52.53183 1.0000000 0.50000000    Norm    Norm
3142     96 1995.150 53.03183 1.5000000 0.50000000    Norm    Norm
NA       NA       NA       NA        NA         NA    <NA>    <NA>
NA.1     NA       NA       NA        NA         NA    <NA>    <NA>
NA.2     NA       NA       NA        NA         NA    <NA>    <NA>
NA.3     NA       NA       NA        NA         NA    <NA>    <NA>
```



```
> subset(L4, lex.id == 159)[,1:7]
         per      age        tfi    lex.dur lex.Cst lex.Xst lex.id
646 1994.025 67.49624  0.0000000  0.1341547     Mic     Mic    159
647 1994.159 67.63039  0.1341547  2.6639288     Mic    Norm    159
648 1996.823 70.29432  2.7980835  2.3737166    Norm     Mic    159
649 1999.196 72.66804  5.1718001  7.3210130     Mic     Mac    159
650 2006.517 79.98905 12.4928131  3.9479808     Mac  D(CVD)    159
> subset(S4, lex.id == 159)[c(1:2,NA,6:7,NA,12:13,NA,27:28,NA,36:37),1:7]
     lex.id      per      age        tfi    lex.dur lex.Cst lex.Xst
4853    159 1994.025 67.49624  0.0000000  0.1341547     Mic     Mic
4854    159 1994.159 67.63039  0.1341547  0.3658453     Mic     Mic
NA       NA       NA       NA         NA         NA    <NA>    <NA>
4858    159 1996.025 69.49624  2.0000000  0.5000000     Mic     Mic
4859    159 1996.525 69.99624  2.5000000  0.2980835     Mic    Norm
NA.1     NA       NA       NA         NA         NA    <NA>    <NA>
4864    159 1998.525 71.99624  4.5000000  0.5000000    Norm    Norm
4865    159 1999.025 72.49624  5.0000000  0.1718001    Norm     Mic
NA.2     NA       NA       NA         NA         NA    <NA>    <NA>
4879    159 2005.525 78.99624 11.5000000  0.5000000     Mic     Mic
4880    159 2006.025 79.49624 12.0000000  0.4928131     Mic     Mac
NA.3     NA       NA       NA         NA         NA    <NA>    <NA>
4888    159 2009.525 82.99624 15.5000000  0.5000000     Mac     Mac
4889    159 2010.025 83.49624 16.0000000  0.4407940     Mac  D(CVD)
```

How the split works



Same amount of follow-up

Same transitions

More intervals (5, resp. 37)

Different value of time scales between intervals

Purpose of the split

- Assumption of constant rate in each interval
- All intervals are (shorter than) 0.5 years
- Magnitude of the rates depend on covariates:
  - fixed covariates
  - time scales
  - randomly varying covariates (not now)
- value of covaraites differ between intervals
- each record contributes one term to the (log-)likelihood for a specific rate
  `from` a given origin state (`lex.Cst`)
  `to` a given destination state (`lex.Cst`).
- —looks as the likelihood for a single Poisson observation

Modeling the rate: `Mic -> D(CVD)`

```
> mr <- glm(cbind(lex.Xst == "D(CVD)" & lex.Cst != lex.Xst,
+                 lex.dur)
+           ~ Ns(tfi, knots = seq( 0, 20, 5)) +
+             Ns(age, knots = seq(50, 80, 10)),
+           family = poisreg,
+             data = subset(S4, lex.Cst == "Mic"))
```

. . . the same as:

```
> mp <- glm((lex.Xst == "D(CVD)" & lex.Cst != lex.Xst)
+           ~ Ns(tfi, knots = seq( 0, 20, 5)) +
+             Ns(age, knots = seq(50, 80, 10)),
+           offset = log(lex.dur),
+           family = poisson,
+             data = subset(S4, lex.Cst == "Mic"))
> summary(coef(mr) - coef(mp))
      Min.    1st Qu.     Median       Mean    3rd Qu.       Max.
-1.368e-12 -2.364e-13 -2.887e-14 -1.625e-13 -7.883e-15  6.839e-13
```


Modeling the rate: `Mic -> D(CVD)`

A convenient wrapper for `Lexis` objects:

```
> mL <- glm.Lexis(S4,
+                 ~ Ns(tfi, knots = seq( 0, 20, 5)) +
+                   Ns(age, knots = seq(50, 80, 10)),
+                 from = "Mic",
+                   to = "D(CVD)")
stats::glm Poisson analysis of Lexis object S4 with log link:
Rates for the transition: Mic->D(CVD)
> summary(coef(mr) - coef(mL))
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
      0       0       0       0       0       0
```


`glm.Lexis` by default models all transitions `to` absorbing states, `from` states preceding these

```
> mX <- glm.Lexis(S4,
+                 ~ Ns(tfi, knots = seq( 0, 20, 5)) +
+                   Ns(age, knots = seq(50, 80, 10)) +
+                   lex.Cst)
stats::glm Poisson analysis of Lexis object S4 with log link:
Rates for transitions: Norm->D(CVD), Mic->D(CVD), Mac->D(CVD), Norm->D(oth), Mic-
```

Describe the model(s) in `mX`:

- What rates are modeled ?
- How are they modeled (assumptions about shapes) ?
- What are the differences between the rates modeled?
- What would you rather do?