Multistate models:

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

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R installed

We will be using the `Epi` package

```
> library(Epi)
> library(tidyverse)
```

and sometimes also fundtions from the `tidyverse` package — but beware some conflicts exist

R is a calculator—use the console

```
> 3 + 2

[1] 5

> x <- 3 * 7
> x

[1] 21

> 5 / 12 -> z
> z

[1] 0.4166667
```

R operates on **objects** — vectors, data frames, models etc.

Everyting is a function

Fit a regression model

```
> m1 <- lm(y ~ x, data = dd)
```

uses the variables `y` and `x` from the data frame `dd` and saves the result in `m1`, `m1` is an object of **class** `lm`

But it prints nothing.

You get the result printed by typing the name of the object:

```
> m1

Call:
lm(formula = y ~ x, data = dd)

Coefficients:
(Intercept)            x
    -2.6360       0.3888
```

A `summary` method exists for some objects

```
> summary(m1)

Call:
lm(formula = y ~ x, data = dd)

Residuals:
     Min       1Q   Median       3Q      Max
-0.83379 -0.31168 -0.06909  0.30041  0.87754

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) -2.63598    0.21710  -12.14 3.05e-16
x            0.38882    0.02847   13.66  < 2e-16

Residual standard error: 0.4394 on 48 degrees of freedom
Multiple R-squared:  0.7954, Adjusted R-squared:  0.7911
F-statistic: 186.6 on 1 and 48 DF,  p-value: < 2.2e-16
```

A `str` method exists for all objects

```
> str(m1)

List of 12
 $ coefficients : Named num [1:2] -2.636 0.389
  ..- attr(*, "names")= chr [1:2] "(Intercept)" "x"
 $ residuals    : Named num [1:50] 0.597 0.878 0.499 0.112 0.142 ...
  ..- attr(*, "names")= chr [1:50] "1" "2" "3" "4" ...
 $ effects      : Named num [1:50] -1.4519 6.0016 0.49 -0.0472 0.1142 ...
  ..- attr(*, "names")= chr [1:50] "(Intercept)" "x" "" "" ...
 $ rank         : int 2
 $ fitted.values: Named num [1:50] -0.5893 0.0796 0.5955 -0.5328 0.4572 ...
  ..- attr(*, "names")= chr [1:50] "1" "2" "3" "4" ...
 $ assign       : int [1:2] 0 1
 $ qr           :List of 5
  ..$ qr   : num [1:50, 1:2] -7.071 0.141 0.141 0.141 0.141 ...
  .. ..- attr(*, "dimnames")=List of 2
  .. .. ..$ : chr [1:50] "1" "2" "3" "4" ...
  .. .. ..$ : chr [1:2] "(Intercept)" "x"
  .. ..- attr(*, "assign")= int [1:2] 0 1
  ..$ qraux: num [1:2] 1.14 1
  ..$ pivot: int [1:2] 1 2
```

When something goes wrong

. . . you want to see how your data looks — is it as you expected?

Use these functions to see what you have:

```
> summary(dd)
> str(dd)
> dim(dd)
> length(dd)
> names(dd)
> class(dd)
> mode(dd)
```

You can create your own functions

Calculate logit (log-odds) from probability:

```
> p2l <- function(pr)
+         {
+         odds <- log(pr / (1 - pr))
+         odds
+         }
```

function name is `p2l` (`p`robability `2` `l`ogit)
argument name is `pr`
function value is the value of the last expression in the
function body (which is what is between the `{}`s):

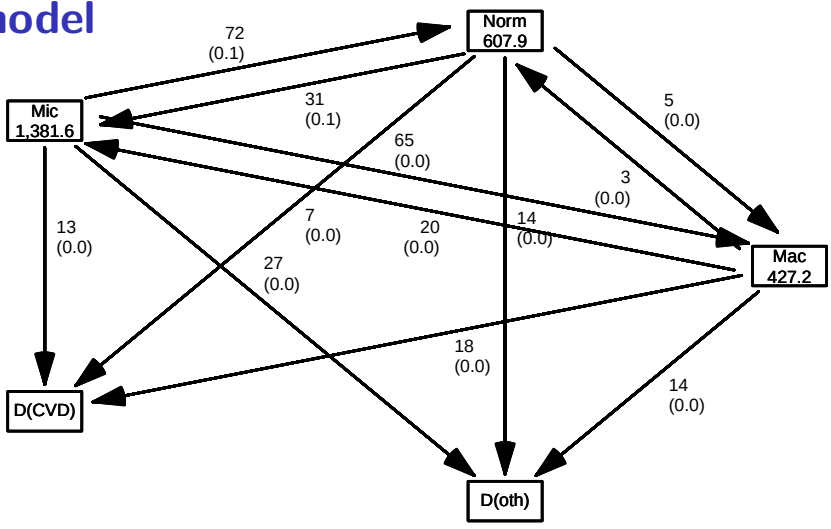
```
> p2l(p = 0.37)
```

```
[1] -0.5322168
```

argument **value** is `0.37`

Your turn — practicals chapter 1!

A multistate model



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- Not really a model
- What is the data
- What are the target parameters?

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    ...same as:
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  - State probabilities (of being in a state at a given time)
  - Survival probability
  - Sojourn times (how long does the year spend in a state)
  - Probability of ever visiting a state

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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 the likelihood of data is the statistical model
- ⇒ Estimation of parameters in the model
- Parameter estimates needed for prediction of rates (hazards)

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Survival data

Persons enter the study at some date.

Persons exit at a later date, either dead or alive.

Observation:
Actual time span to death (“event”)
or
Some time alive (“at least this long”)

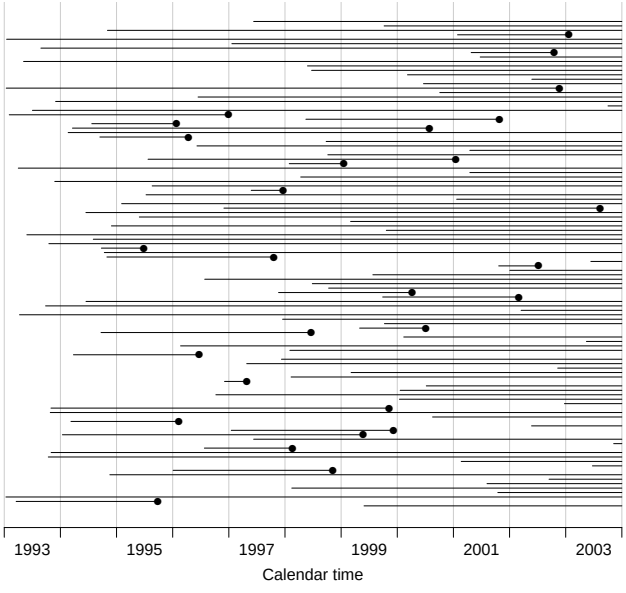
Examples of time-to-event measurements

- Time from diagnosis of cancer to death.
- Time from randomisation to death in a cancer clinical trial
- Time from HIV infection to AIDS.
- Time from marriage to 1st child birth.
- Time from marriage to divorce.
- Time to re-offending after being released from jail

Each line a person

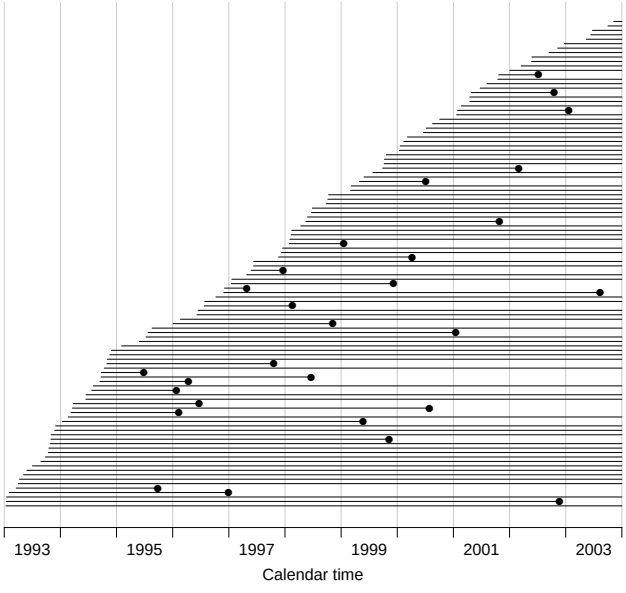
Each blob a death

Study ended at 31 Dec. 2003

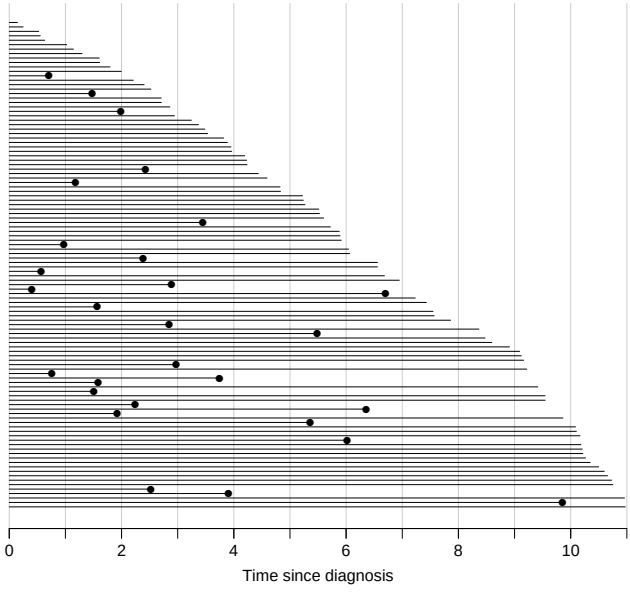


Ordered by date of entry

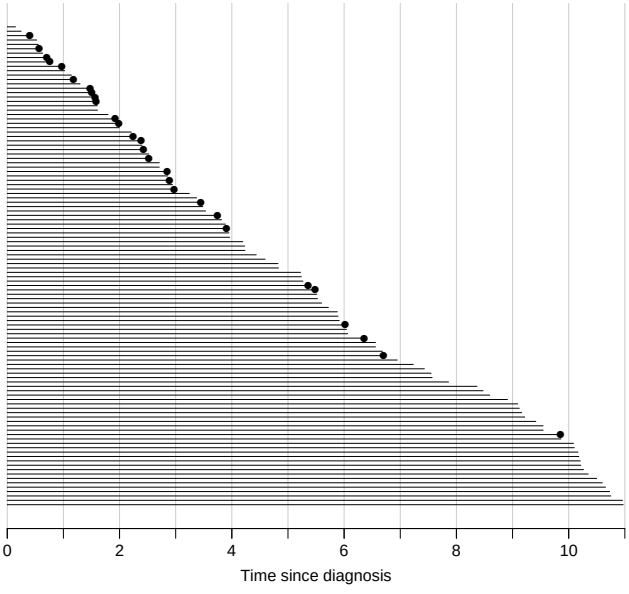
Most likely the order in your database.



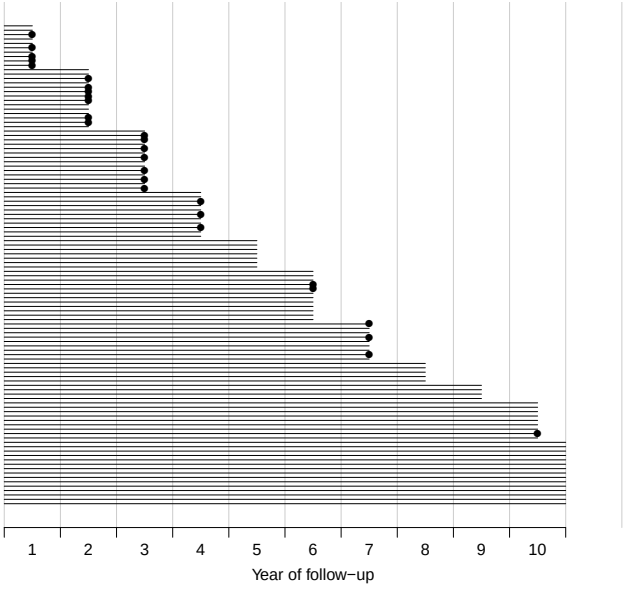
Timescale changed to "Time since diagnosis".



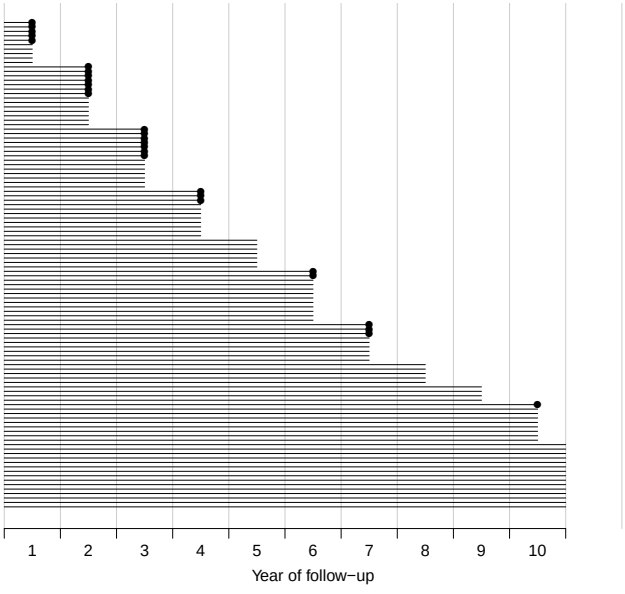
Patients ordered by survival time.



Survival times grouped into bands of survival.



Patients ordered by survival status within each band.



Survival after Cervix cancer

	Stage I			Stage II		
Year	N	D	L	N	D	L
1	110	5	5	234	24	3
2	100	7	7	207	27	11
3	86	7	7	169	31	9
4	72	3	8	129	17	7
5	61	0	7	105	7	13
6	54	2	10	85	6	6
7	42	3	6	73	5	6
8	33	0	5	62	3	10
9	28	0	4	49	2	13
10	24	1	8	34	4	6

Life-table estimator of death probability: $D/(N - L/2)$

Estimated risk of death in year 1 for Stage I women is $5/107.5 = 0.0465$

Estimated 1 year survival is $1 - 0.0465 = 0.9535$

Survival after Cervix cancer

	Stage I			Stage II		
Year	N	D	L	N	D	L
1	110	5	5	234	24	3
2	100	7	7	207	27	11
3	86	7	7	169	31	9

Estimated risk in year 1 for Stage I women is $5/107.5 = 0.0465$
Estimated risk in year 2 for Stage I women is $7/96.5 = 0.0725$
Estimated risk in year 3 for Stage I women is $7/82.5 = 0.0848$

Estimated 1 year survival is $1 - 0.0465 = 0.9535$
Estimated 2 year survival is $0.9535 \times (1 - 0.0725) = 0.8843$
Estimated 3 year survival is $0.8843 \times (1 - 0.0848) = 0.8093$

This is the life-table estimator.

- No need to use 1 year intervals
- Very small intervals will leave at most 1 censoring or 1 death in each
- Interval with 1 death and n_t persons at risk:
  $\mathrm{P}\{\text{Death}\} = 1/n_t$
- corresponding death probability $(n_t - 1)/n_t$
- if you multiply these over times with event:

$$S(t) = \prod_{t \text{ with event}} (n_t - 1)/n_t$$

  . . . you have the **Kaplan-Meier estimator**
- looks complicated bút just a question of book keeping

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
 228.00  165.00   10.18    9.36   11.93
> # 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?

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

     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
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```

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 ph.ka
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
  meal.cal wt.loss
1     1175      NA
2     1225      15
3       NA      15
```

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`: `C`urrent `st`ate, the state in which the `lex.dur` time is spent.

`lex.Xst`: e`X`it `st`ate, 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.

`Lexis` object: Overview of follow-up

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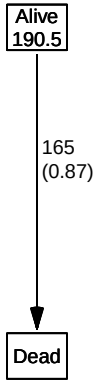
```
> summary(L1)

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 = Ll)
```

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

Using the Lexis features:

```
> cL <- coxph.Lexis(Ll, tfl ~ sex + age)

survival::coxph analysis of Lexis object Ll:
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 = Ll)
```

or even simpler, by using the `Lexis` features:

```
> pL <- glm.Lexis(Ll, ~ sex + age)

stats::glm Poisson analysis of Lexis object Ll 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.

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 $\lambda(t) = \lambda$:

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

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:

$$\Pr\{\text{survive } t_e \text{ to } t_x\} = \prod_{j=0}^{N-1} \left(1 - \frac{\lambda_j y}{N}\right)^N$$

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$$\mathbb{P}\{\text{survive } t_e \text{ to } t_x\} \approx 0 - Mh = \left(1 - \frac{\lambda y}{N}\right)^N$$

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- 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:

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

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 $N \to \infty$:

$$P(\text{survive } t_0 \text{ to } t_0) \approx \left(1 - \frac{\lambda y}{N}\right)^N \to \exp(-\lambda y), \quad N \to \infty \tag{2}$$

- 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 $-\lambda y$.

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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
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  - log-likelihood contribution from this last instant is $\log(\lambda\epsilon) = \log(\lambda) + \log(\epsilon)$.

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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

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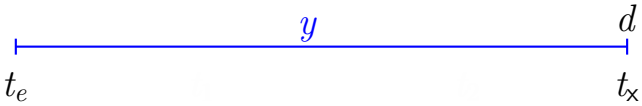
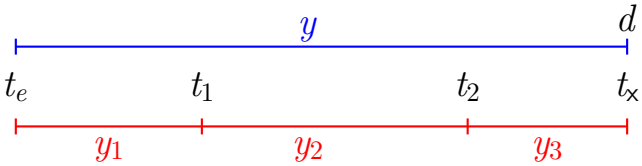


Probability

$\mathrm{P}(d \text{ at } t_x | \text{entry } t_e)$

log-Likelihood

$d \log(\lambda) - \lambda y$



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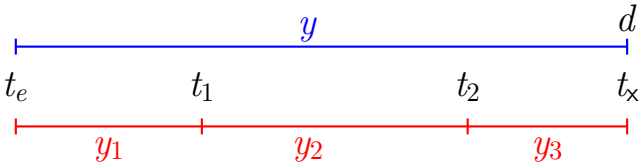


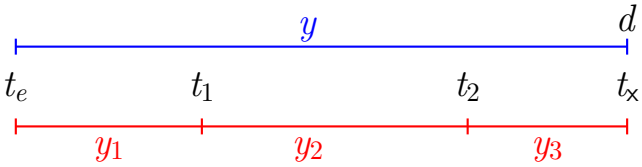
Probability

$\mathrm{P}(d \text{ at } t_x | \text{entry } t_e)$

$= \mathrm{P}(\text{surv } t_e \to t_1 | \text{entry } t_e)$

log-Likelihood

$d \log(\lambda) - \lambda y$



Probability

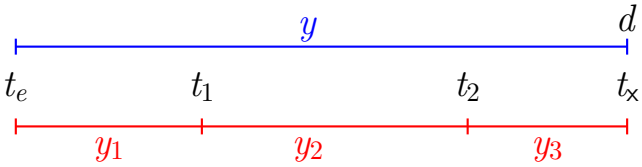
$\mathrm{P}(d \text{ at } t_x | \text{entry } t_e)$

$= \mathrm{P}(\text{surv } t_e \to t_1 | \text{entry } t_e)$

$\times \mathrm{P}(\text{surv } t_1 \to t_2 | \text{entry } t_1)$

log-Likelihood

$d \log(\lambda) - \lambda y$



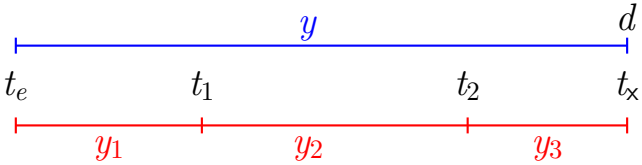
Probability

$\mathrm{P}(d \text{ at } t_x | \text{entry } t_e)$

$= \mathrm{P}(\text{surv } t_e \to t_1 | \text{entry } t_e)$
$\times \mathrm{P}(\text{surv } t_1 \to t_2 | \text{entry } t_1)$
$\times \mathrm{P}(d \text{ at } t_x | \text{entry } t_2)$

log-Likelihood

$d \log(\lambda) - \lambda y$



Probability

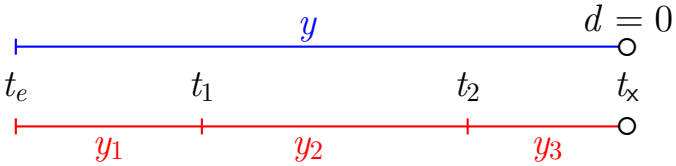
$\mathrm{P}(d \text{ at } t_x | \text{entry } t_e)$

$= \mathrm{P}(\text{surv } t_e \to t_1 | \text{entry } t_e)$
$\times \mathrm{P}(\text{surv } t_1 \to t_2 | \text{entry } t_1)$
$\times \mathrm{P}(d \text{ at } t_x | \text{entry } t_2)$

log-Likelihood

$d \log(\lambda) - \lambda y$

$= 0 \log(\lambda) - \lambda y_1$
$+ 0 \log(\lambda) - \lambda y_2$
$+ d \log(\lambda) - \lambda y_3$



Probability

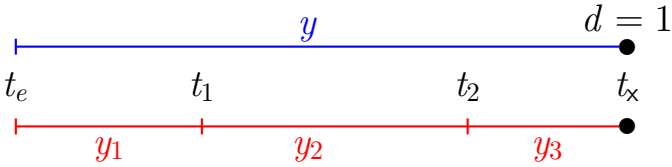
$$\mathrm{P}(\text{surv } t_e \to t_x | \text{entry } t_e)$$

$$= \mathrm{P}(\text{surv } t_e \to t_1 | \text{entry } t_e)$$
$$\times \mathrm{P}(\text{surv } t_1 \to t_2 | \text{entry } t_1)$$
$$\times \mathrm{P}(\text{surv } t_2 \to t_x | \text{entry } t_2)$$

log-Likelihood

$$0 \log(\lambda) - \lambda y$$

$$= 0 \log(\lambda) - \lambda y_1$$
$$+ 0 \log(\lambda) - \lambda y_2$$
$$+ 0 \log(\lambda) - \lambda y_3$$



Probability

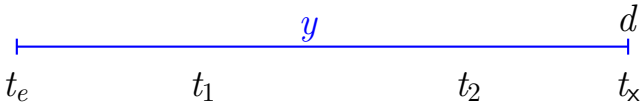
$\mathrm{P}(\text{event at } t_x | \text{entry } t_e)$

$= \mathrm{P}(\text{surv } t_e \to t_1 | \text{entry } t_e)$
$\times \mathrm{P}(\text{surv } t_1 \to t_2 | \text{entry } t_1)$
$\times \mathrm{P}(\text{event at } t_x | \text{entry } t_2)$

log-Likelihood

$1 \log(\lambda) - \lambda y$

$= 0 \log(\lambda) - \lambda y_1$
$+ 0 \log(\lambda) - \lambda y_2$
$+ 1 \log(\lambda) - \lambda y_3$



Probability

$\mathrm{P}(d \text{ at } t_x | \text{entry } t_e)$

$= \mathrm{P}(\text{surv } t_e \to t_1 | \text{entry } t_e)$
$\times \mathrm{P}(\text{surv } t_1 \to t_2 | \text{entry } t_1)$
$\times \mathrm{P}(d \text{ at } t_x | \text{entry } t_2)$

log-Likelihood

$d \log(\lambda) - \lambda y$

$= 0 \log(\lambda) - \lambda y_1$
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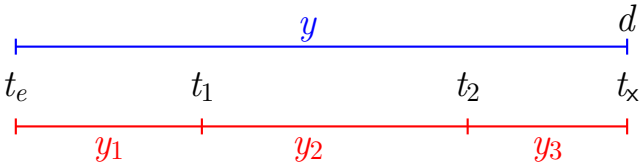

Probability

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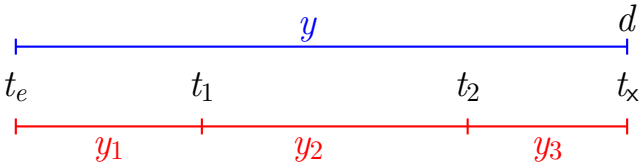

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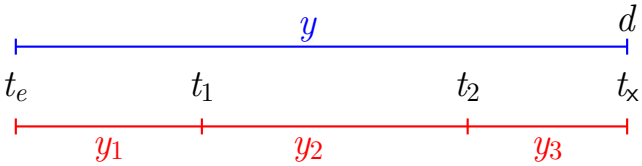
$$\times \mathrm{P}(d \text{ at } t_x | \text{entry } t_2)$$

log-Likelihood

$$d \log(\lambda) - \lambda y$$

$$= 0 \log(\lambda_1) - \lambda_1 y_1$$
$$+ 0 \log(\lambda_2) - \lambda_2 y_2$$
$$+ d \log(\lambda_3) - \lambda_3 y_3$$

– allows different rates (λ_i) in each interval



Probability

$$\mathrm{P}(d \text{ at } t_x | \text{entry } t_e)$$
$$= \mathrm{P}(\text{surv } t_e \to t_1 | \text{entry } t_e)$$
$$\times \mathrm{P}(\text{surv } t_1 \to t_2 | \text{entry } t_1)$$
$$\times \mathrm{P}(d \text{ at } t_x | \text{entry } t_2)$$

log-Likelihood

$$d \log(\lambda) - \lambda y$$
$$= 0 \log(\lambda_1) - \lambda_1 y_1$$
$$+ 0 \log(\lambda_2) - \lambda_2 y_2$$
$$+ d \log(\lambda_3) - \lambda_3 y_3$$

— allows different rates (λ_i) in each interval

Baseline hazard: splitting time

```
> S1 <- splitMulti(L1, tf1 = 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(Ll)[1:10] # names of variables in some order
> subset(Ll, 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(Sl, 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 `Sl` 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 = Sl)
```

or even simpler:

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

stats::glm Poisson analysis of Lexis object Sl 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(cl),
+             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?

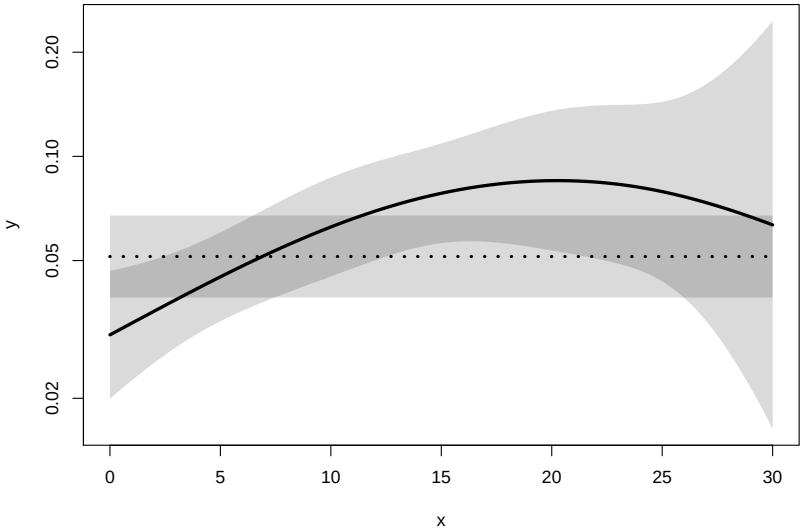
ps is a model for the hazard so we can predict the value of it at defined values for the covariates in the model:

```
> 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

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

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...

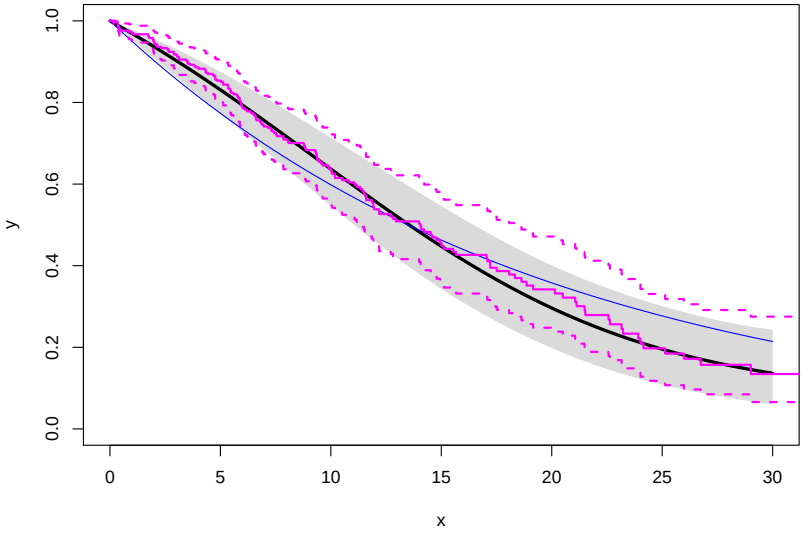
Implemented in the `ci.surv` function

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")
```

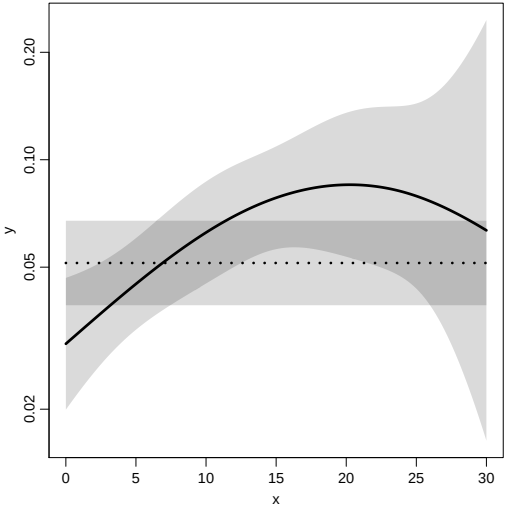
Survival functions

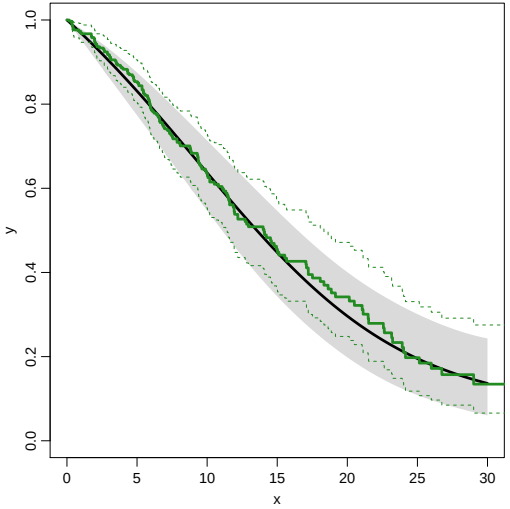


Hazard and survival functions

```
> 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



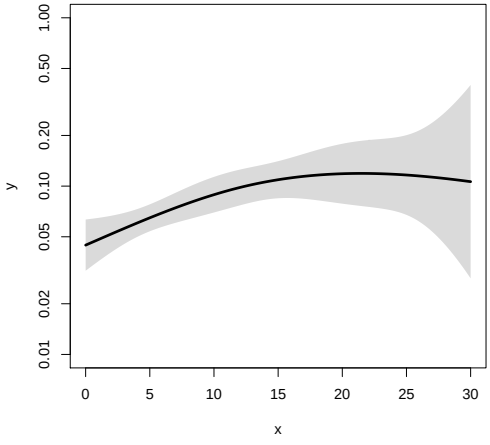


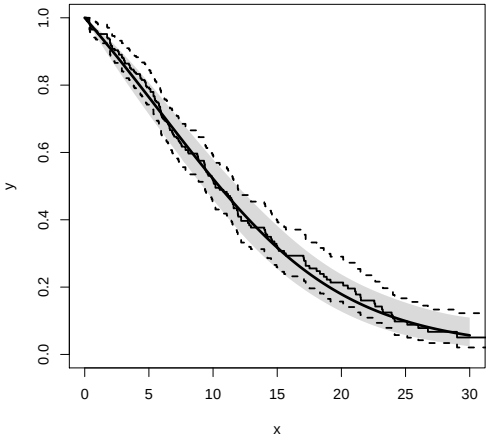
K-M estimator and smooth Poisson model

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



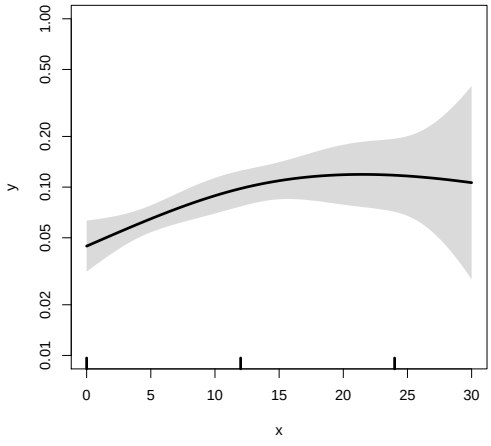


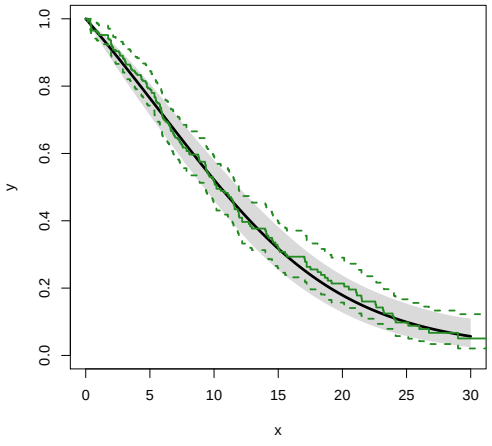
K-M estimator and smooth Poisson model

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

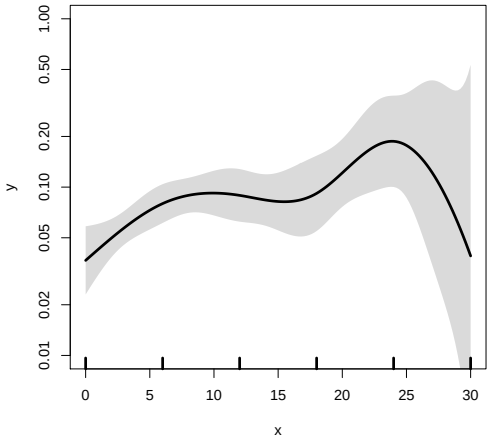
```
> zz <- function(dk) # distance between knots
+ {
+ par(mfrow=c(1,2))
+ kn <- seq(0, 36, dk)
+ pk <- glm(cbind(lex.Xst == "Dead",
+                 lex.dur) ~ Ns(tfl, knots = kn),
+           family = poisreg,
+             data = Sl)
+ matshade(prf$tfl, ci.pred(pk, prf),
+          plot = TRUE,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

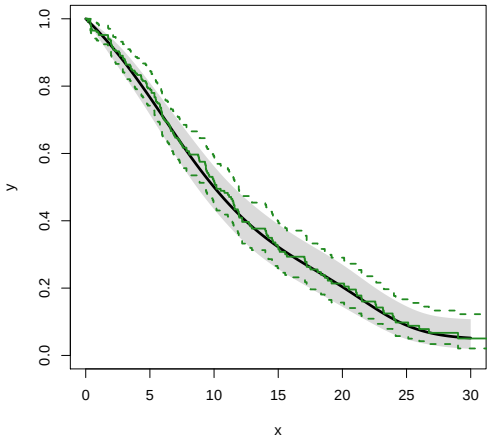
K-M estimator and smooth Poisson model



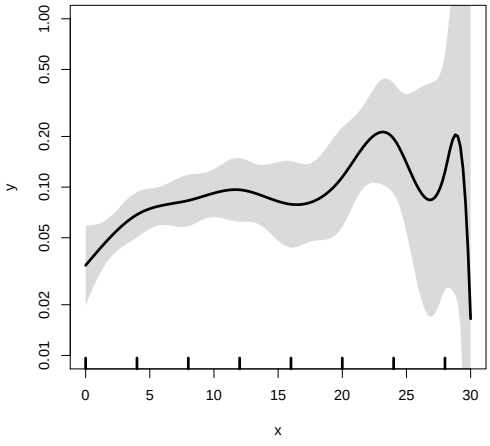


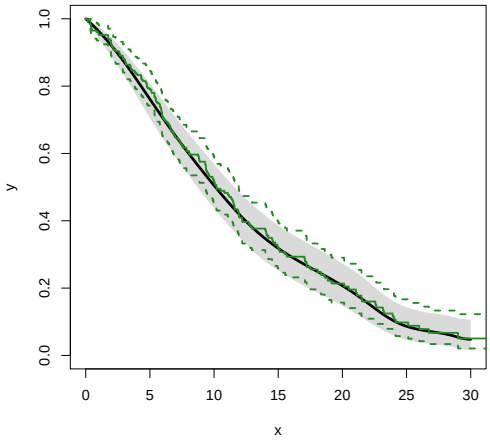
K-M estimator and smooth Poisson model



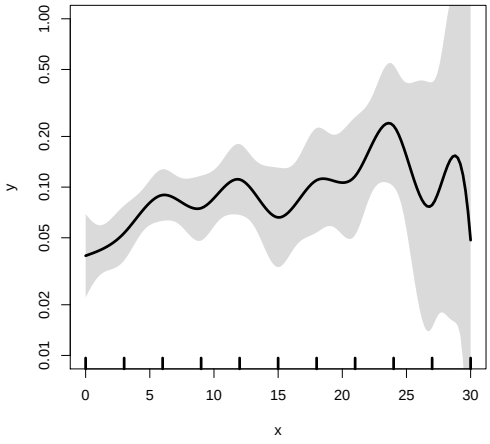


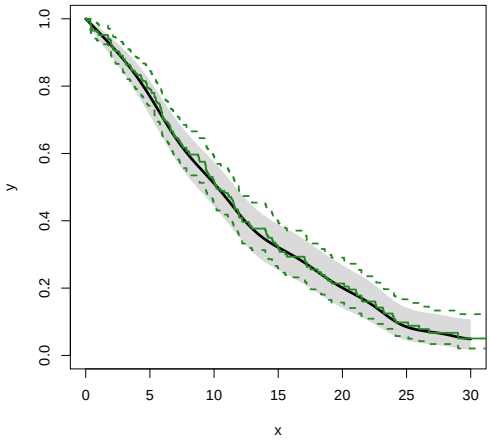
K-M estimator and smooth Poisson model



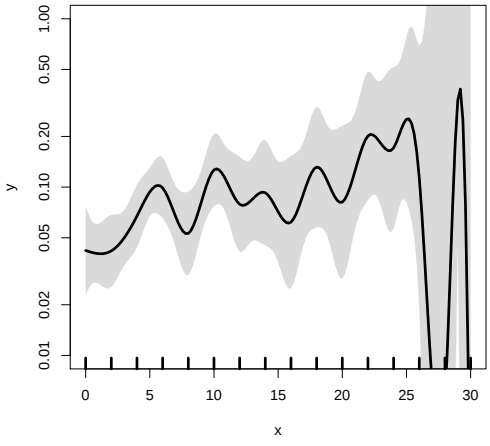


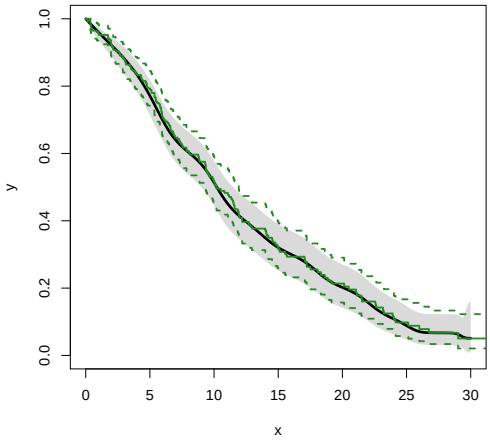
K-M estimator and smooth Poisson model



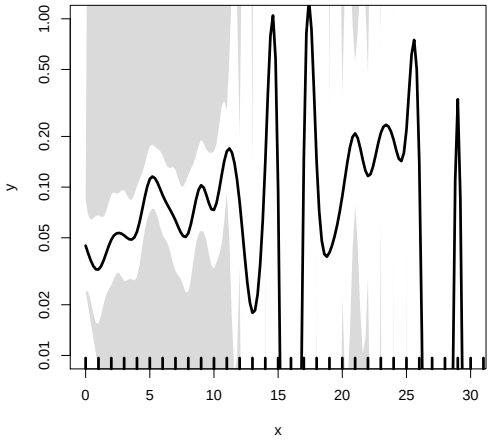


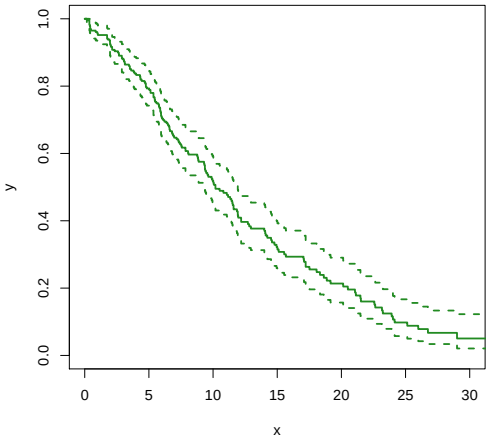
K-M estimator and smooth Poisson model





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 ...
```

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
```

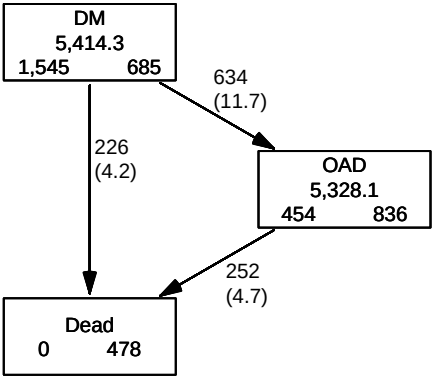
Cut follow-up at the date of OAD, dooad

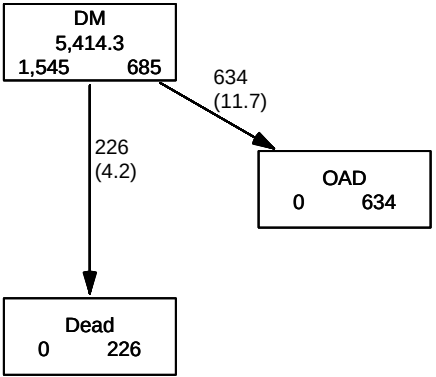
```
> subset(Ldm, lex.id %in% c(2:3,20))[,c(1:7,12)]

          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?

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

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` $\rightarrow$ `Dead`
- **Competing risks**: what is the probability of being in each of the states `DM`, `OAD` and `Dead`
  —depends on **two** rates, `DM` $\rightarrow$ `OAD` and `DM` $\rightarrow$ `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
```

Survival function and cumulative risks—formulae

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

Survival function and cumulative risks—formulae

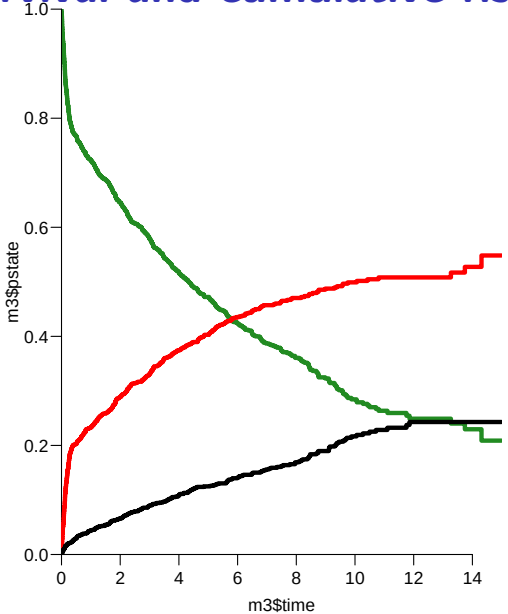
$$
\begin{aligned}
S(t) &= \exp\Big(-\int_0^t \lambda(u) + \mu(u)\,\mathrm{d}u\Big) \\
R_{\texttt{Dead}}(t) &= \int_0^t \mu(u) S(u)\,\mathrm{d}u \\
R_{\texttt{OAD}}(t) &= \int_0^t \lambda(u) S(u)\,\mathrm{d}u) \\
&= \int_0^t \lambda(u) \exp\Big(-\int_0^u \lambda(s) + \mu(s)\,\mathrm{d}s\Big)\,\mathrm{d}u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

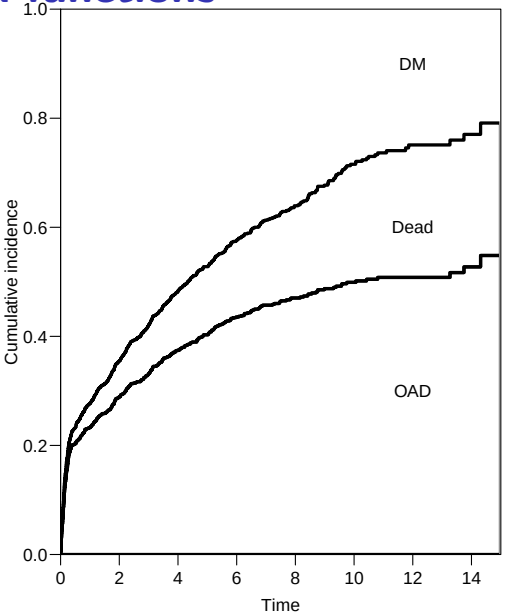
$$
S(t) + R_{\texttt{OAD}}(t) + R_{\texttt{Dead}}(t) = 1, \quad \forall t
$$

Survival function and cumulative risks

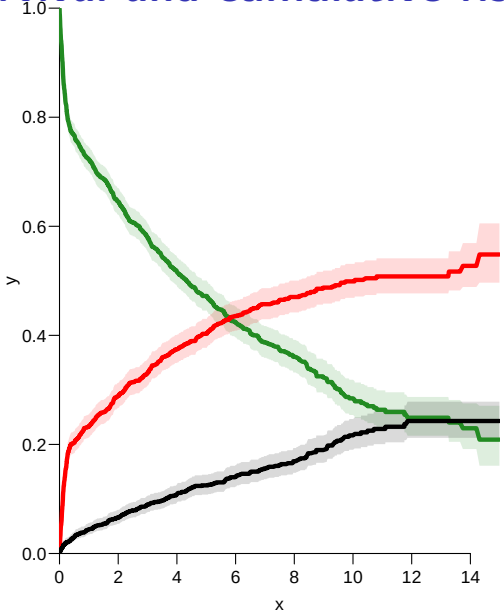
```
> par( mfrow=c(1,2) )
> matplot(m3$time, m3$pstate,
+         type="s", lty=1, lwd=4,
+         col=c("ForestGreen","red","black"),
+         xlim=c(0,15), xaxs="i",
+         ylim=c(0,1), yaxs="i" )
> stackedCIF(m3, lwd=3, xlim=c(0,15), xaxs="i", yaxs="i" )
> text(rep(12,3), c(0.9,0.3,0.6), levels(Cdm))
> 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")
```

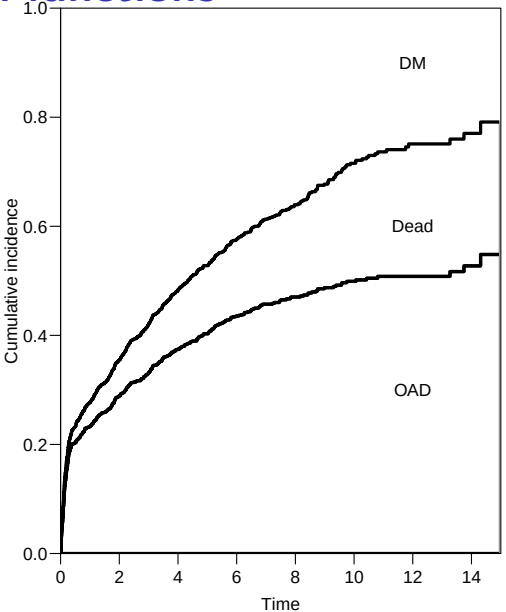
Survival and cumulative risk functions





Survival and cumulative risk functions





Survival function and cumulative risks—don't

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

but I wonder, but wrong!

Probability of DAD according Dead does not exist and rate of DAD unchanged!

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 DAD according Dead does not exist and rate of DAD unchanged!

Survival function and cumulative risks—don't

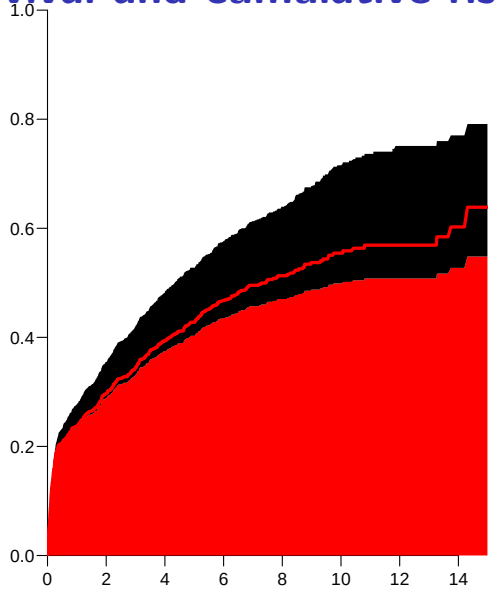
$$
\begin{aligned}
S(t) &= \exp\Big(-\int_0^t \lambda(u) + \mu(u)\,\mathrm{d}u\Big) \\
R_{\texttt{Dead}}(t) &= \int_0^t \mu(u) S(u)\,\mathrm{d}u \\
R_{\texttt{OAD}}(t) &= \int_0^t \lambda(u) S(u)\,\mathrm{d}u) \\
&= \int_0^t \lambda(u) \exp\Big(-\int_0^u \lambda(s) + \mu(s)\,\mathrm{d}s\Big)\,\mathrm{d}u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

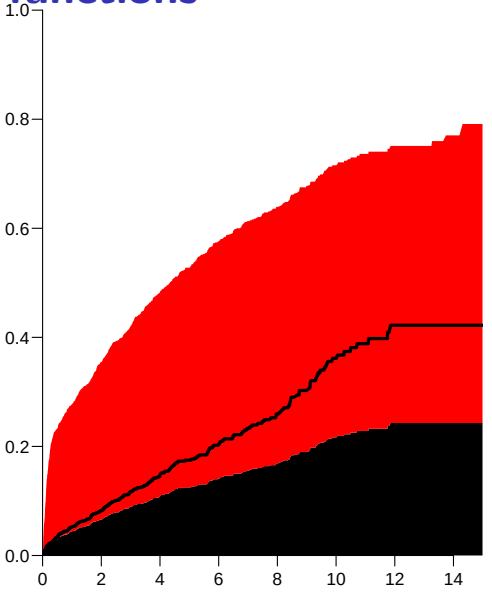
Probability of `OAD` **assuming** `Dead` does not exist **and** rate of `OAD` unchanged!

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
```

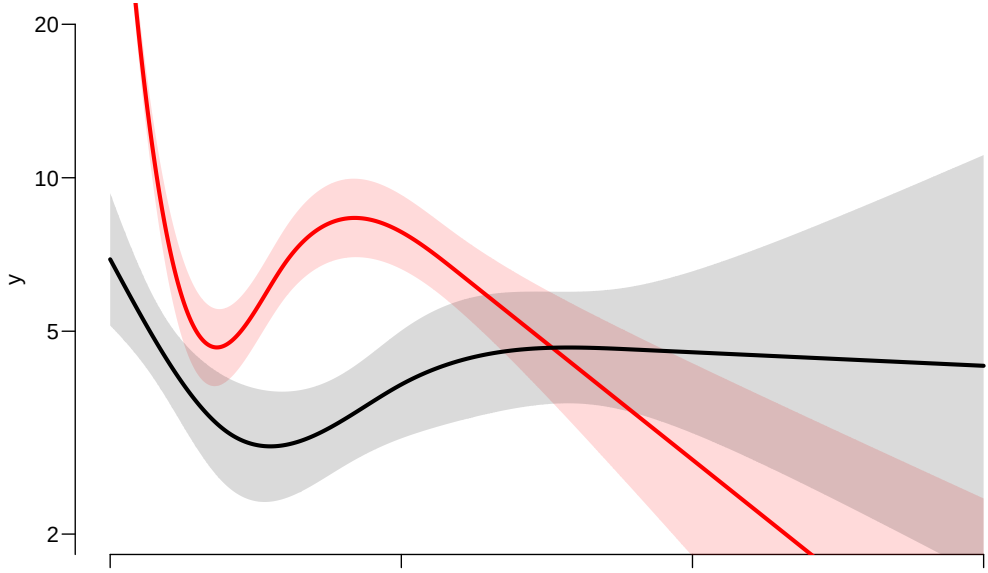
Cause-specific rates

```
> 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
```

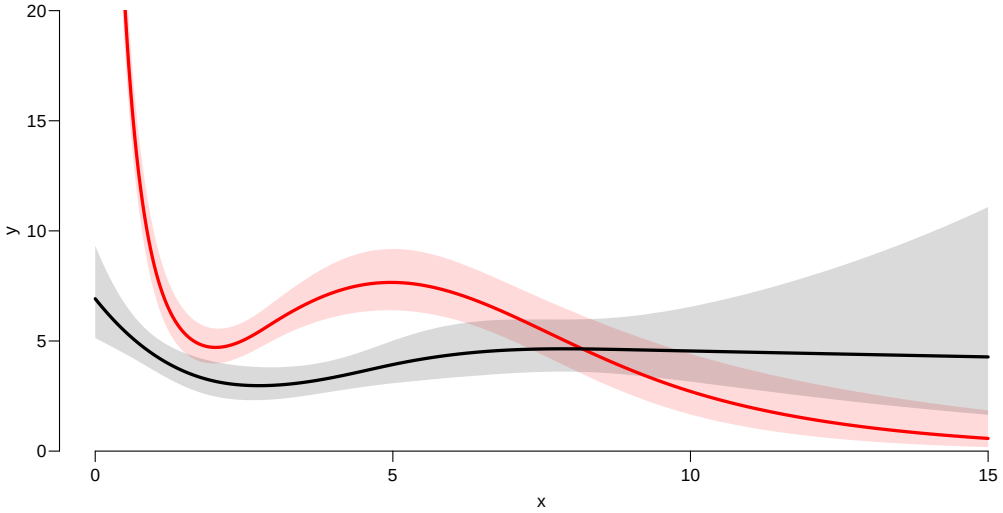
Cause-specific rates

```
> 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



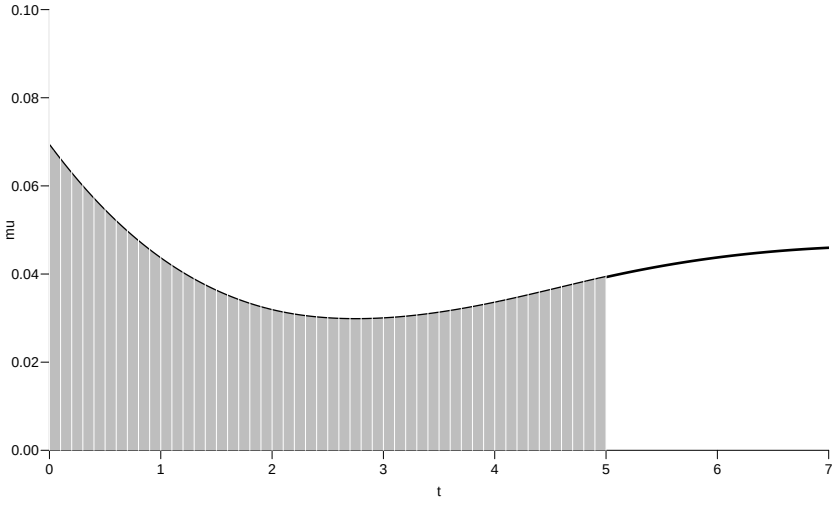
Integrals with R

- 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 (≈ 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

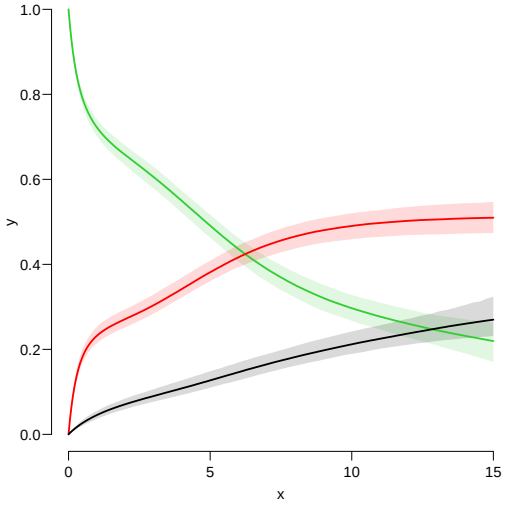
```
> cR <- ci.Crisk(mods = list(OAD =  OAD.glm,
+                            Dead = Dead.glm),
+                    nd = nd)

NOTE: Times are assumed to be in the column tfd at equal distances of 0.01

> str(cR)

List of 4
 $ Crisk: num [1:1501, 1:3, 1:3] 1 0.992 0.984 0.976 0.969 ...
  ..- attr(*, "dimnames")=List of 3
  .. ..$ tfd  : chr [1:1501] "0" "0.01" "0.02" "0.03" ...
  .. ..$ cause: chr [1:3] "Surv" "OAD" "Dead"
  .. ..$      : chr [1:3] "50%" "2.5%" "97.5%"
 $ Srisk: num [1:1501, 1:2, 1:3] 0 0.000692 0.001375 0.002049 0.002715 ...
  ..- attr(*, "dimnames")=List of 3
  .. ..$ tfd  : chr [1:1501] "0" "0.01" "0.02" "0.03" ...
  .. ..$ cause: chr [1:2] "Dead" "Dead+OAD"
  .. ..$      : chr [1:3] "50%" "2.5%" "97.5%"
 $ Stime: num [1:1501, 1:3, 1:3] 0 0.00996 0.01984 0.02964 0.03937 ...
  ..- attr(*, "dimnames")=List of 3
  .. ..$ tfd  : chr [1:1501] "0" "0.01" "0.02" "0.03" ...
```

Cumulative risks from parametric models

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

```
> matshade(cR$time, cbind(cR$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)

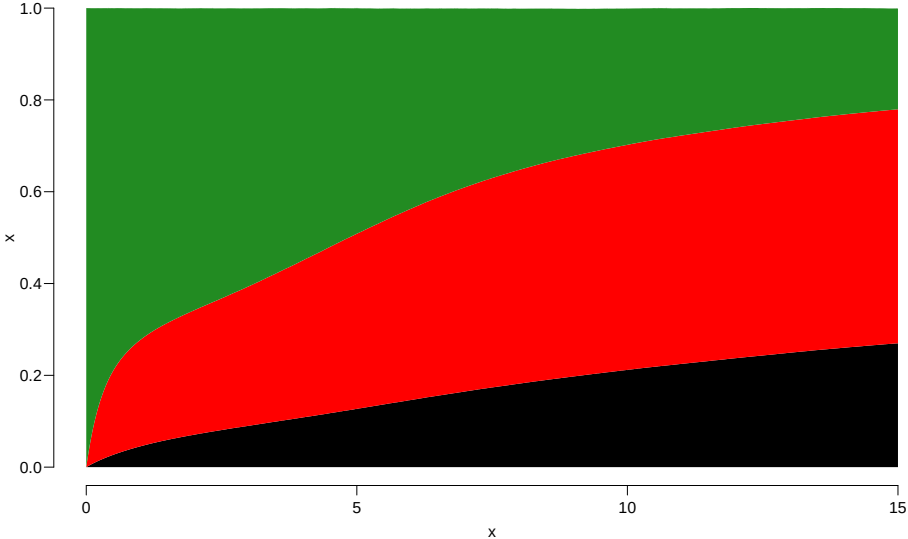
```
> mat2pol(cR$Crisk[,3:1,1], col = c("forestgreen","red","black")[3:1])
```

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

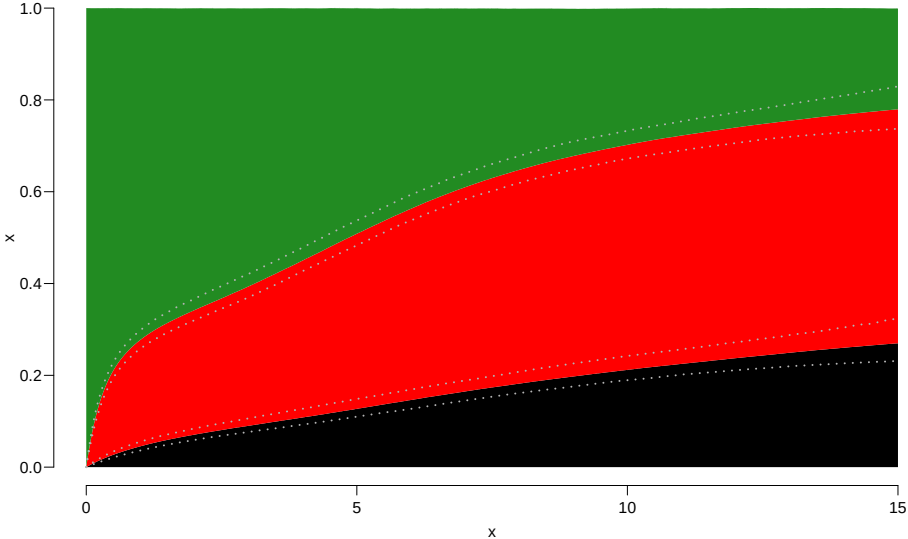
The component `Srisk` has the confidence limits of the stacked probabilities:

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

Survival and cumulative risk functions



Survival and cumulative risk functions



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` (Sojourn `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 0.00996 0.01984 0.02964 0.03937 ...
 - attr(*, "dimnames")=List of 3
  ..$ tfd  : chr [1:1501] "0" "0.01" "0.02" "0.03" ...
  ..$ cause: chr [1:3] "Surv" "OAD" "Dead"
  ..$      : chr [1:3] "50%" "2.5%" "97.5%"

> round(cR$Stime[c("5","10","15"),"Surv",], 1)

tfd  50% 2.5% 97.5%
  5  3.2  3.1   3.3
  10 5.1  4.9   5.3
  15 6.4  6.0   6.7
```

Background: Steno 2 trial

- Clinical trial for diabetes ptt. with kidney disease (micro-albuminuria)
- 160 ptt. randomised 1:1 to either of
  - Conventional treatment
  - Intensified multifactorial treament
- Recuitment 1993–1994
- Trial period 1993–2001
- Latest 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

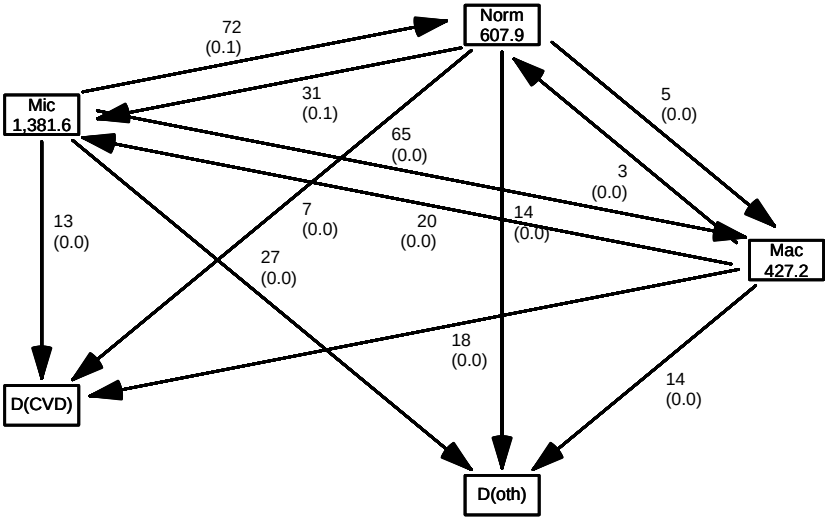
```
> data(st2alb) ; head(st2alb, 3)

  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

```
> L2$per <- as.numeric(L2$per)
> cut2$cut <- as.numeric(cut2$cut)
> 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
```

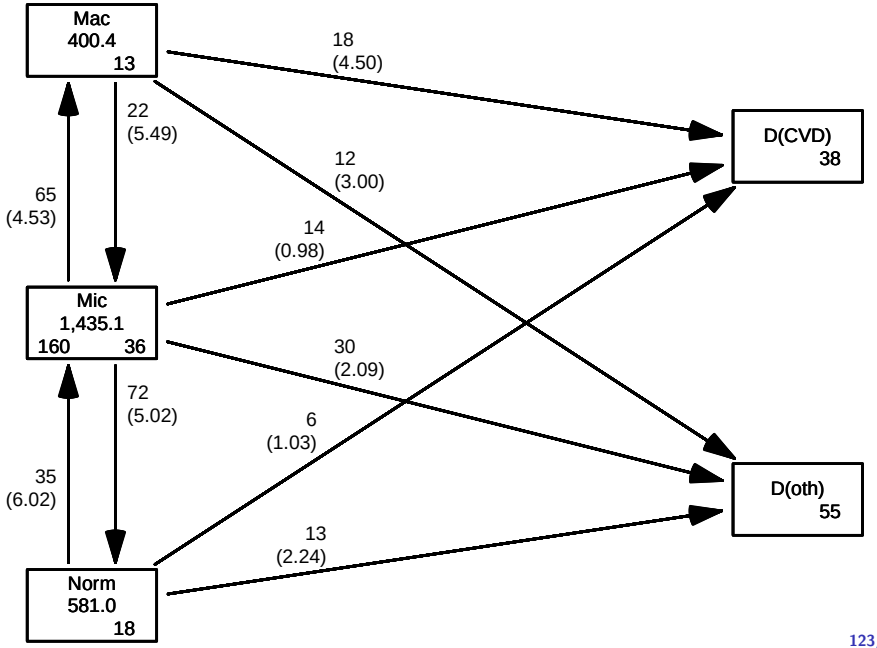
—and what will you do about it?

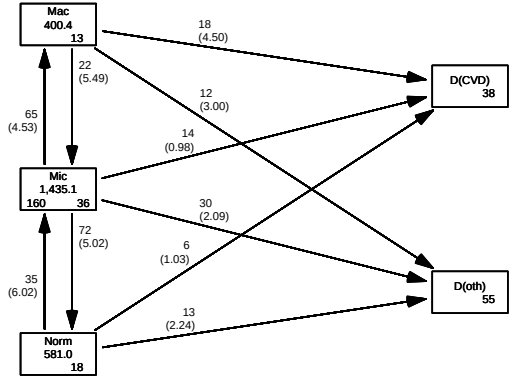
How to fix things

```
> 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)
```


Mac
400.4
13
Mic
1,435.1
160 36
Norm
581.0
18
D(CVD)
38
D(oth)
55
18
(4.50)
22
(5.49)
65
(4.53)
12
(3.00)
14
(0.98)
30
(2.09)
72
(5.02)
6
(1.03)
35
(6.02)
13
(2.24)



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(..., split_at = popEpi)`
  - Compare the `Lexis` objects

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

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,17:19),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>
3154	96	2000.150	58.03183	6.5000000	0.50000000	Norm	Norm
3155	96	2000.650	58.53183	7.0000000	0.50000000	Norm	Norm
3156	96	2001.150	59.03183	7.5000000	0.33299110	Norm	D(CVD)

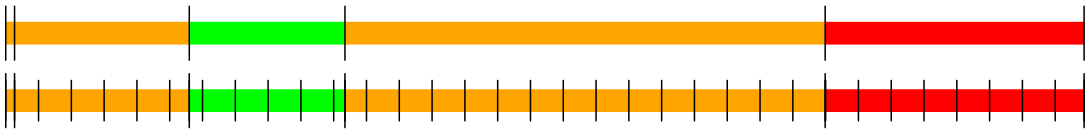
```
> subset(L4, lex.id == 159)[,1:7]
```

	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
  - value of some covariates differ between intervals
  - each record contributes one term to the (log-)likelihood for a specific rate
    from a given origin state (`lex.Cat`)
    to a given destination state (`lex.Xst`)
  - $\leftarrow$ looks as the likelihood for a single Poisson observation

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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 some covariates 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.Xst`)
- enters as the likelihood for a single Poisson observation

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
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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
  - (currently varying covariates (not now))
- value of some covariates 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.Xst`)
- =⇒ looks as the likelihood for a single Poisson observation

Purpose of the split

- Assumption of constant rate in each interval
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  - fixed covariates
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- each record contributes one term to the (log-)likelihood for a specific rate
  `from` a given origin state (`lex.Cst`)
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- Looks as the likelihood for a single Poisson observation

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  - fixed covariates
  - time scales
  - randomly varying covariates (not now)
- value of some covariates 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.Xst`).
- —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.
-1.315e-12 -2.389e-13 -2.343e-14 -1.540e-13  7.050e-15  6.466e-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?

```
> mox <- glm.Lexis(S4, ~ Ns(tfi, knots = seq( 0, 20, 5)) +
+                        Ns(age, knots = seq(50, 80, 10)) +
+                        lex.Cst / allo,
+                  to = "D(oth)")

stats::glm Poisson analysis of Lexis object S4 with log link:
Rates for transitions: Norm->D(oth), Mic->D(oth), Mac->D(oth)

> mCx <- glm.Lexis(S4, ~ Ns(tfi, knots = seq( 0, 20, 5)) +
+                        Ns(age, knots = seq(50, 80, 10)) +
+                        lex.Cst / allo,
+                  to = "D(CVD)")

stats::glm Poisson analysis of Lexis object S4 with log link:
Rates for transitions: Norm->D(CVD), Mic->D(CVD), Mac->D(CVD)
```

```
> det <- glm.Lexis(S4, ~ Ns(tfi, knots = seq( 0, 20, 5)) +
+                        Ns(age, knots = seq(50, 80, 10)) +
+                        lex.Cst / allo,
+                  from = c("Norm","Mic"),
+                    to = c("Mic","Mac"))

stats::glm Poisson analysis of Lexis object S4 with log link:
Rates for transitions: Norm->Mic, Mic->Mac

> imp <- glm.Lexis(S4, ~ Ns(tfi, knots = seq( 0, 20, 5)) +
+                        Ns(age, knots = seq(50, 80, 10)) +
+                        lex.Cst / allo,
+                  from = c("Mac","Mic"),
+                    to = c("Mic","Norm"))

stats::glm Poisson analysis of Lexis object S4 with log link:
Rates for transitions: Mac->Mic, Mic->Norm
```

Specification of the model

```
> Tr <- list(Norm = list("Mic" = det,
+                        "D(oth)" = mox,
+                        "D(CVD)" = mCx),
+             Mic = list("Mac" = det,
+                        "Norm" = imp,
+                        "D(oth)" = mox,
+                        "D(CVD)" = mCx),
+             Mac = list("Mic" = imp,
+                        "D(oth)" = mox,
+                        "D(CVD)" = mCx))
> lapply(Tr, names)

$Norm
[1] "Mic"    "D(oth)" "D(CVD)"

$Mic
[1] "Mac"    "Norm"   "D(oth)" "D(CVD)"

$Mac
[1] "Mic"    "D(oth)" "D(CVD)"
```

Specification of the prediction population

A population that looks like the original Steno2 population.

```
> ini <- L2[,c("per", "age", "tfi")]
> ini <- rbind(transform(ini, lex.Cst = factor("Mic"), allo = factor("Int")),
+              transform(ini, lex.Cst = factor("Mic"), allo = factor("Conv")))
> ini$lex.Cst <- factor(ini$lex.Cst, levels = levels(L4))
> str(ini)

Classes 'Lexis' and 'data.frame': 320 obs. of  5 variables:
 $ per    : num  1993 1993 1993 1993 1993 ...
 $ age    : 'cal.yr' num  61.1 46.6 49.9 48.5 57.3 ...
 $ tfi    : num  0 0 0 0 0 0 0 0 0 0 ...
 $ lex.Cst: Factor w/ 5 levels "Norm","Mic","Mac",..: 2 2 2 2 2 2 2 2 2 2 ...
 $ allo   : Factor w/ 2 levels "Int","Conv": 1 1 1 1 1 1 1 1 1 1 ...
 - attr(*, "breaks")=List of 3
  ..$ per: NULL
  ..$ age: NULL
  ..$ tfi: NULL
 - attr(*, "time.scales")= chr  "per" "age" "tfi"
 - attr(*, "time.since")= chr  "" "" ""
```

Simulating a cohort

```
> set.seed(1952)
> system.time(
+ Sorg <- simLexis(Tr = Tr,  # models for each transition
+                   init = ini, # cohort of straters
+                      N = 10,  # how many copies of each person in ini
+                t.range = 20,  # how long should we simulate before censoring
+                  n.int = 100))# how many intervals for evaluating rates

   user  system elapsed
 18.745   8.848  16.851
```

Simulated cohort

```
> summary(Sorg)

Transitions:
     To
From   Norm  Mic  Mac D(CVD) D(oth)  Records:  Events: Risk time:  Persons:
  Norm  387  655    0    114    266       1422    1035   11582.90       1300
  Mic  1422  646 1302    281    574       4225    3579   26869.84       3200
  Mac     0  370  308    383    241       1302     994    7831.63       1206
  Sum  1809 1671 1610    778   1081       6949    5608   46284.38       3200
```

How many are where, when?

```
> Nst <- nState(Sorg,
+                 at = seq(0, 20, 0.2),
+               from = 0,
+         time.scale = "tfi")
> str(Nst)
```

```
 'table' int [1:101, 1:5] 0 88 167 233 295 341 389 443 500 542 ...
 - attr(*, "dimnames")=List of 2
  ..$ when : chr [1:101] "0" "0.2" "0.4" "0.6" ...
  ..$ State: chr [1:5] "Norm" "Mic" "Mac" "D(CVD)" ...
```

```
> head(Nst)
```

```
     State
when  Norm  Mic  Mac D(CVD) D(oth)
  0      0 3200    0      0      0
  0.2   88 3077   33      2      0
  0.4  167 2966   62      5      0
  0.6  233 2863   98      6      0
  0.8  295 2772  120     13      0
  1    341 2693  148     17      1
```

Who is where when?

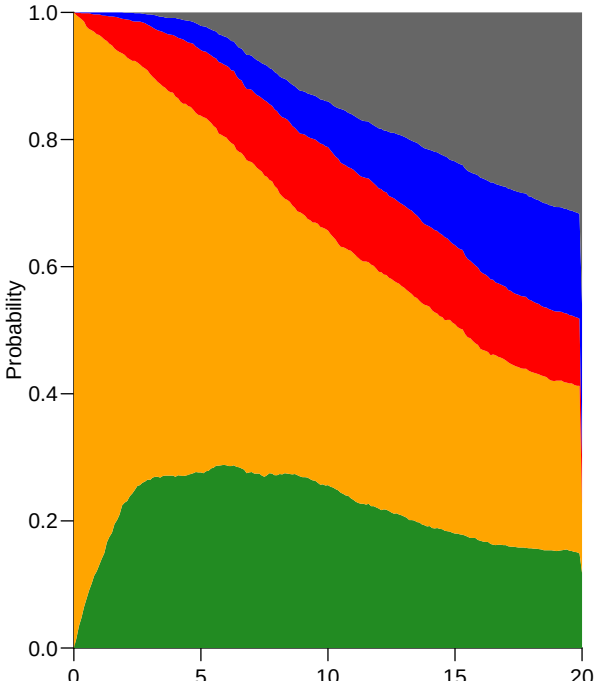
```
> Nint <- nState(subset(Sorg, allo == "Int"),
+                at = seq(0, 20, 0.1),
+              from = 0,
+       time.scale = "tfi")
> Nconv<- nState(subset(Sorg, allo == "Conv"),
+                at = seq(0, 20, 0.1),
+              from = 0,
+       time.scale = "tfi")
> head(Nint , 4)

     State
when  Norm  Mic  Mac D(CVD) D(oth)
  0      0 1600    0      0      0
  0.1   24 1569    6      1      0
  0.2   55 1533   11      1      0
  0.3   76 1507   15      2      0

> head(Nconv, 4)

     State
when  Norm  Mic  Mac D(CVD) D(oth)
  0      0 1600    0      0      0
```

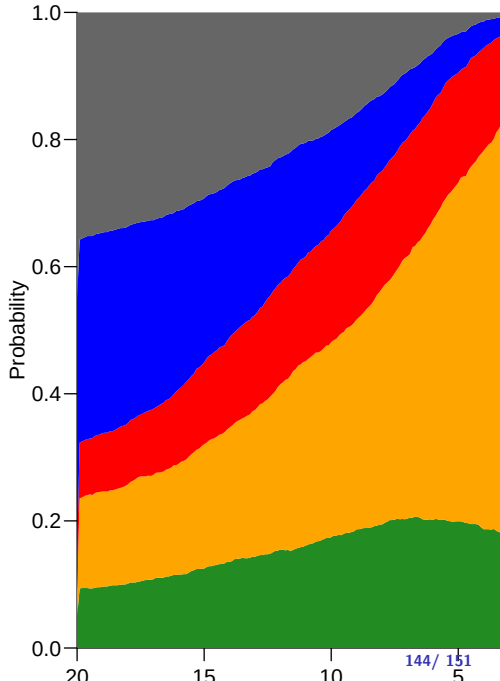
Cumulative proportions (state probabilities)

```
> Pint  <- pState(Nint )
> Pconv <- pState(Nconv)
>  str(Pint)

 'pState' num [1:201, 1:5] 0 0.015 0.0344 0.0475 0.0644 ...
 - attr(*, "dimnames")=List of 2
  ..$ when : chr [1:201] "0" "0.1" "0.2" "0.3" ...
  ..$ State: chr [1:5] "Norm" "Mic" "Mac" "D(CVD)" ...

> head(Pint)

     State
when      Norm      Mic      Mac D(CVD) D(oth)
  0   0.000000 1.000000 1.000000      1      1
  0.1 0.015000 0.995625 0.999375      1      1
  0.2 0.034375 0.992500 0.999375      1      1
  0.3 0.047500 0.989375 0.998750      1      1
  0.4 0.064375 0.985625 0.998750      1      1
  0.5 0.077500 0.977500 0.998750      1      1
```

Standard plotting of the state probs

```
> clr <- c("forestgreen", "orange", "red", "blue", gray(0.4))
> par(mfrow = c(1,2), mar=c(3,3,2,2))
> plot(Pint, col = clr, xlim = c(0, 20))
> plot(Pconv, col = clr, xlim = c(20, 0))
```


1.0
0.8
0.6
0.4
0.2
0.0
Probability
0
5
10
15
20


1.0
0.8
0.6
0.4
0.2
0.0
Probability
20
15
10
5

What now?

- Initial population:
  The probabilities refer to a population of patienst with the same age-composition as the original Steno2 population.
- We can get an estimate of this using the Aalen-Johansen estimator ()
- But we can get something better by using a different initial population:
- A set of prespecified ages

A different initial population

`ini` must be a `Lexis` object — hence the copy from `S4`

```
> ini <- S4[1:10,c("lex.id", "per", "age", "tfi", "lex.Cst", "allo")]
> ini[,"lex.id"]  <- 1:10
> ini[,"per"]     <- 1993 # not used but it is a time scale in S4
> ini[,"age"]     <-
+ ini[,"ain"]     <- rep(seq(45,65,5), 2)
> ini[,"tfi"]     <- 0
> ini[,"lex.Cst"] <- factor("Mic",
+                           levels = c("Norm","Mic","Mac","D(CVD)","D(oth)"))
> ini[,"allo"]    <- factor(rep(c("Int","Conv"), each = 5))
> ini
```

```
   lex.id  per age tfi lex.Cst allo ain
1       1 1993  45   0     Mic  Int  45
2       2 1993  50   0     Mic  Int  50
3       3 1993  55   0     Mic  Int  55
4       4 1993  60   0     Mic  Int  60
5       5 1993  65   0     Mic  Int  65
6       6 1993  45   0     Mic Conv  45
7       7 1993  50   0     Mic Conv  50
8       8 1993  55   0     Mic Conv  55
```

A different initial population

`ini` must be a `Lexis` object

```
> str(ini)

Classes 'Lexis' and 'data.frame': 10 obs. of  7 variables:
 $ lex.id : int  1 2 3 4 5 6 7 8 9 10
 $ per    : num  1993 1993 1993 1993 1993 ...
 $ age    : num  45 50 55 60 65 45 50 55 60 65
 $ tfi    : num  0 0 0 0 0 0 0 0 0 0
 $ lex.Cst: Factor w/ 5 levels "Norm","Mic","Mac",..: 2 2 2 2 2 2 2 2 2 2
 $ allo   : Factor w/ 2 levels "Conv","Int": 2 2 2 2 2 1 1 1 1 1
 $ ain    : num  45 50 55 60 65 45 50 55 60 65
 - attr(*, "time.scales")= chr  "per" "age" "tfi"
 - attr(*, "time.since")= chr  "" "" ""
 - attr(*, "breaks")=List of 3
  ..$ per: NULL
  ..$ age: NULL
  ..$ tfi: num  0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 ...
```

```
> system.time(
+ Sdef <- simLexis(Tr = Tr,
+                  init = ini,
+                     N = 500,
+               t.range = 20,
+                 n.int = 200))

   user  system elapsed
 37.915  14.621  37.666

> # str(Sdef)
> summary(Sdef)

Transitions:
     To
From   Norm  Mic  Mac D(CVD) D(oth)  Records:  Events: Risk time:  Persons:
  Norm  583 1028    0    196    407       2214     1631   17784.05       2028
  Mic  2214 1066 2055    413    879       6627     5561   43245.78       5000
  Mac     0  599  510    582    364       2055     1545   12284.90       1879
  Sum  2797 2693 2565   1191   1650      10896     8737   73314.73       5000
```

Stratified initial population

- Makes little sense to show overall state probabilities
- Only separately for age by allocation
- Nothe that we only have one time scale in the state.plot

Stratified initial population

```
> P45c <- pState(nState(subset(Sdef, ain == 45 & allo == "Conv"),
+                at = seq(0, 20, 0.1),
+              from = 0,
+         time.scale = "tfi"))
> P45i <- pState(nState(subset(Sdef, ain == 45 & allo == "Int"),
+                at = seq(0, 20, 0.1),
+              from = 0,
+         time.scale = "tfi"))
> P50c <- pState(nState(subset(Sdef, ain == 55 & allo == "Conv"),
+                at = seq(0, 20, 0.1),
+              from = 0,
+         time.scale = "tfi"))
> P50i <- pState(nState(subset(Sdef, ain == 55 & allo == "Int"),
+                at = seq(0, 20, 0.1),
+              from = 0,
+         time.scale = "tfi"))
> P55c <- pState(nState(subset(Sdef, ain == 55 & allo == "Conv"),
+                at = seq(0, 20, 0.1),
+              from = 0,
+         time.scale = "tfi"))
> P55i <- pState(nState(subset(Sdef, ain == 55 & allo == "Int"),
```

Time spent in Norm during 20 years

```
> summary(Sdef)

Transitions:
     To
From   Norm  Mic  Mac D(CVD) D(oth)  Records:  Events: Risk time:  Persons:
  Norm  583 1028    0    196    407      2214     1631   17784.05      2028
  Mic  2214 1066 2055    413    879      6627     5561   43245.78      5000
  Mac     0  599  510    582    364      2055     1545   12284.90      1879
  Sum  2797 2693 2565   1191   1650     10896     8737   73314.73      5000

> names(Sdef)

 [1] "lex.id"  "per"     "age"     "tfi"     "lex.dur" "lex.Cst" "lex.Xst" "allo"
 [9] "ain"     "cens"

> with(ini, table(age, allo))

    allo
age  Conv Int
  45    1   1
  50    1   1
  55    1   1
  60    1   1
```