Multistate models:

Occurrence rates, cumulative risks, competing risks, state probabilities with multiple states and time scales using R and Epi::Lexis

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http://BendixCarstensen.com

Baker HDI, 22-23 February 2023

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Acknowledgement

I acknowledge the Traditional Owners of the land on which Baker Institute (Melbourne) resides, the Boon Wurrung peoples of the Yaluk-ut Weelam clan.

I pay my respects to all Elders past, present and future.

Survival and rate data

Rates and Survival

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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
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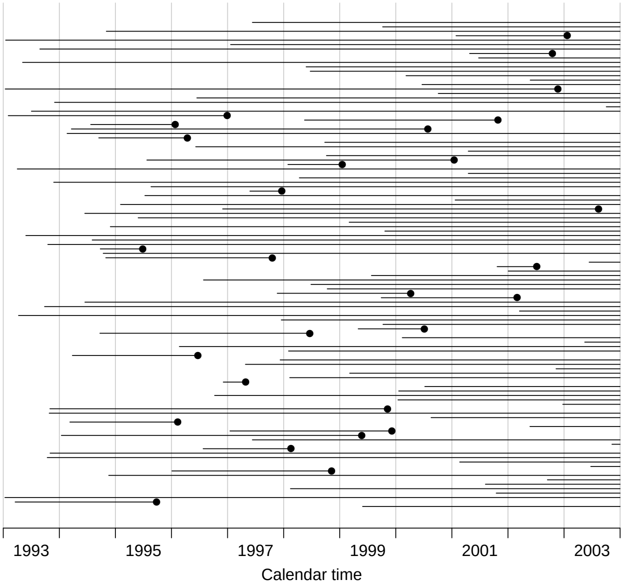
Each line a person

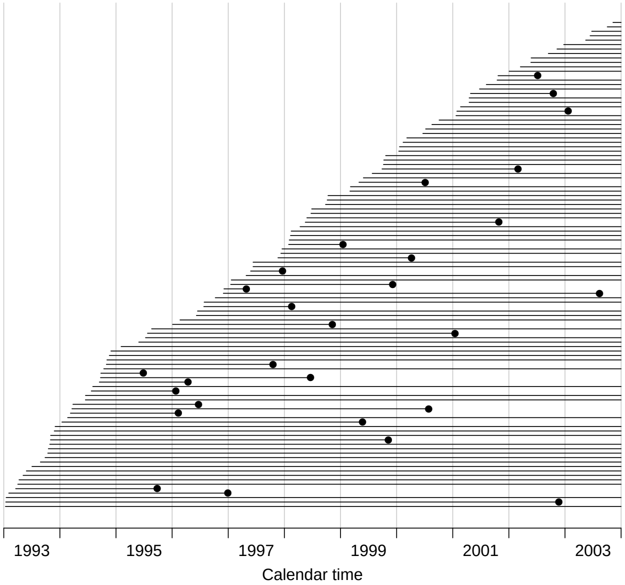
Each blob a death

Study ended at 31 Dec. 2003

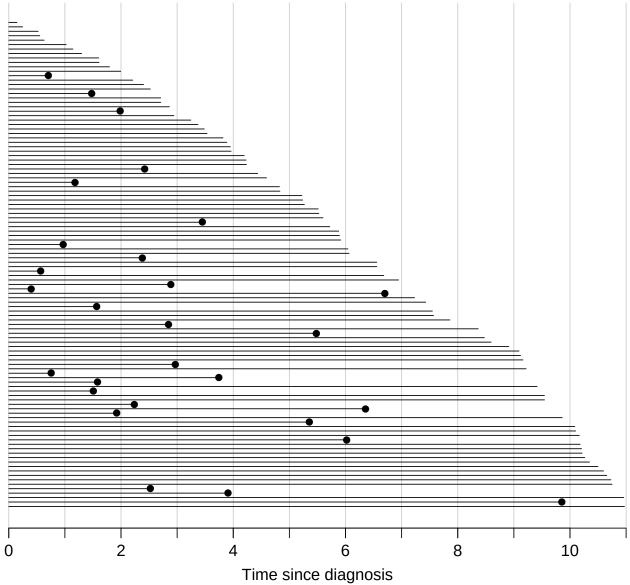


Ordered by date of entry

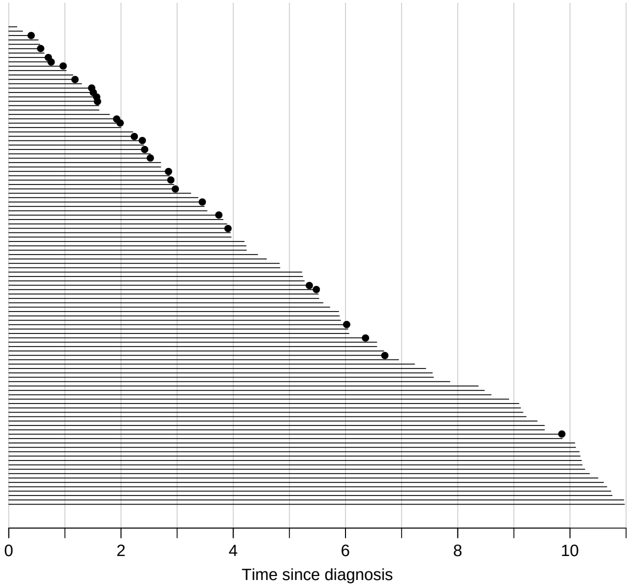
Most likely the order in your database.



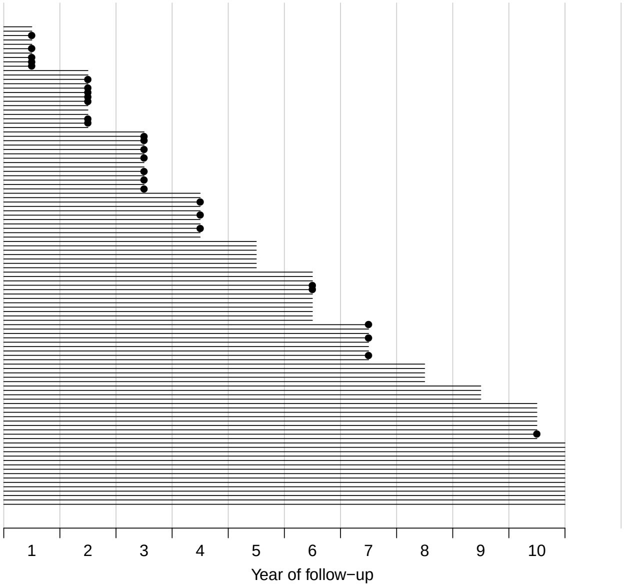
Timescale changed to "Time since diagnosis".



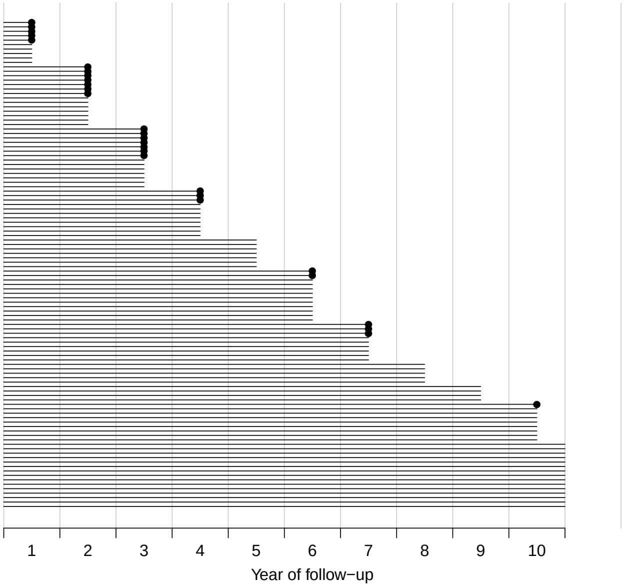
Patients ordered by survival time.



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 $1 - 0.0465 = 0.9535$

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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** of the survival curve.

- no need to use 1 year intervals: 1 day intervals could be used
- very small intervals will leave at most 1 censoring or 1 death in each
- interval with 1 death and n_i persons at risk
  $P\{\text{Death}\} = 1/n_i$
- corresponding survival probability $1 - 1/n_i = (n_i - 1)/n_i$
- interval with 0 deaths has survival probability 1
- multiply these over times with event to get survival function

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

you have the Kaplan-Meier estimator

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…you have the **Kaplan-Meier estimator**

Multistate models

introduction

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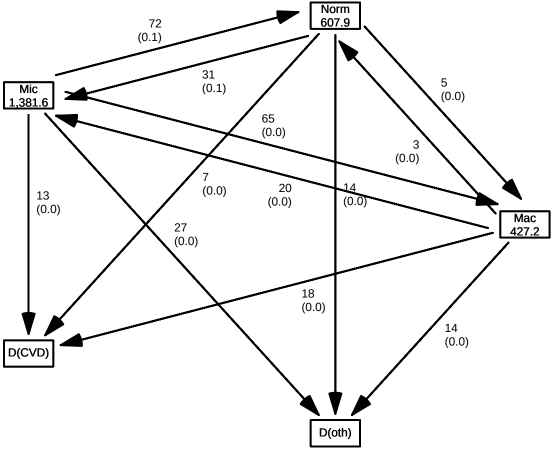
A multistate model



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- Data (observations)

- Time: covariate or response? . . . both, actually:

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- Target parameters:
  - Rates (the arrows)
  - State probabilities (being in a state at a given time)
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  - Sojourn times (how long time do you spend in a state)
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- Specification of a statistical machinery that could have generated data
- …so with a statistical model we can simulate a data set
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Data assumptions

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Lung cancer survival

computations

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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?

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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}

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  —measured in probability per time: time^{-1}
- observation in a survival study: (exit status, time alive)
- empirical rate (d, y) = (deaths, 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

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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)
```

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

$$\begin{aligned}
\mathrm{P}\left\{d \text{ at } t_x \,|\, \text{entry at } t_e\right\} = {} & \mathrm{P}\left\{\text{survive } (t_e, t_1] \,|\, \text{alive at } t_e\right\} \times \\
& \mathrm{P}\left\{\text{survive } (t_1, t_2] \,|\, \text{alive at } t_1\right\} \times \\
& \mathrm{P}\left\{\text{survive } (t_2, t_x] \,|\, \text{alive at } t_2\right\} \times \\
& \mathrm{P}\left\{d \text{ at } t_x \,|\, \text{alive just before } t_x\right\}
\end{aligned}$$

Rates and likelihood

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

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

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

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

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- From mathematics it is known that $(1 + x/n)^n \rightarrow \exp(x)$ as $n \rightarrow \infty$ (some define $\exp(x)$ this way).

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

- 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
- The probability of dying in this tiny instant is $\lambda\epsilon$
- log-likelihood contribution from this last instant is $\log(\lambda\epsilon) = \log(\lambda) + \log(\epsilon)$

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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 the sum of the log-likelihood terms:

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

The last term does not depend on λ and can be ignored.

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Total log-likelihood

- ...for the follow up of 1 person is (the **rate** likelihood):

$$\sum_i \left(d_i \log(\lambda) - \lambda y_i \right)$$

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- even though the d_is are neither Poisson nor independent
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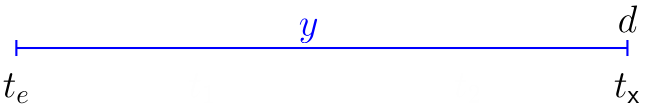
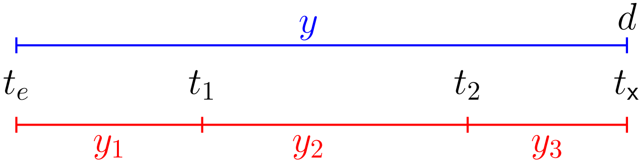


Probability

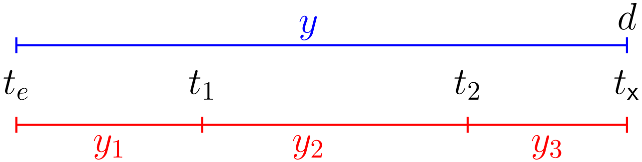
$\mathrm{P}(d \text{ at } t_{\mathsf{x}} | \text{entry } t_e)$

log-Likelihood

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



Probability	log-Likelihood
$P(d \text{ at } t_x \mid \text{entry } t_e)$	$d \log(\lambda) - \lambda y$



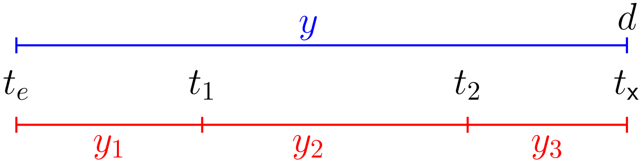
Probability

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

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

log-Likelihood

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



Probability

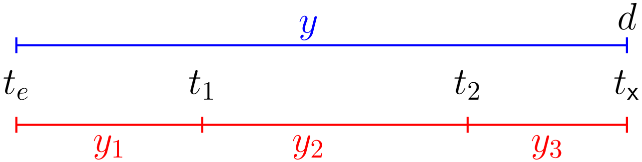
$\mathrm{P}(d \text{ at } t_x | \text{entry } t_e)$

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

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

log-Likelihood

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

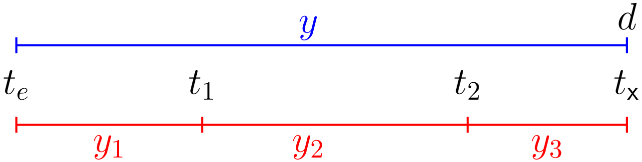


Probability	log-Likelihood
$\mathrm{P}(d \text{ at } t_\mathsf{x} \mid \text{entry } t_e)$	$d \log(\lambda) - \lambda y$

$= \mathrm{P}(\text{surv } t_e \rightarrow t_1 \mid \text{entry } t_e)$

$\times \mathrm{P}(\text{surv } t_1 \rightarrow t_2 \mid \text{entry } t_1)$

$\times \mathrm{P}(d \text{ at } t_\mathsf{x} \mid \text{entry } t_2)$



Probability

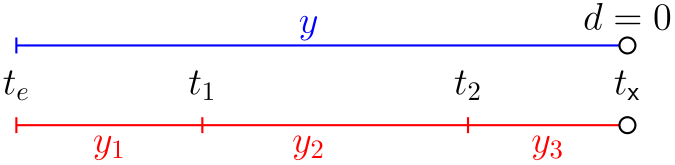
$$\mathrm{P}(d \text{ at } t_\mathsf{x} | \text{entry } t_e)$$

$$= \mathrm{P}(\text{surv } t_e \rightarrow t_1 | \text{entry } t_e)$$
$$\times \mathrm{P}(\text{surv } t_1 \rightarrow t_2 | \text{entry } t_1)$$
$$\times \mathrm{P}(d \text{ at } t_\mathsf{x} | \text{entry } t_2)$$

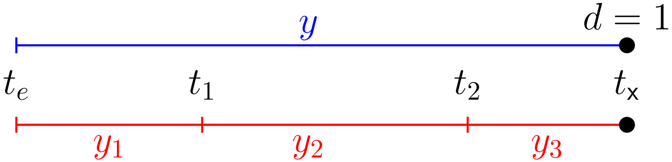
log-Likelihood

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

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



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



Probability

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

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

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

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

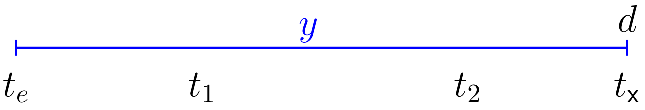
log-Likelihood

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

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

$+ 0 \log(\lambda) - \lambda y_2$

$+ 1 \log(\lambda) - \lambda y_3$



Probability	log-Likelihood
$\mathrm{P}(d \text{ at } t_\mathsf{x} \mid \text{entry } t_e)$	$d \log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_e \to t_1 \mid \text{entry } t_e)$	$= 0 \log(\lambda) - \lambda y_1$
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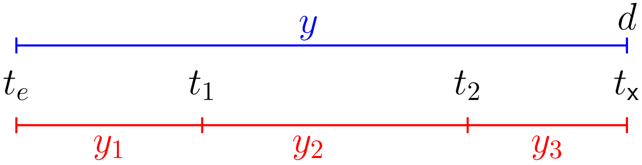


Probability

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

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

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

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

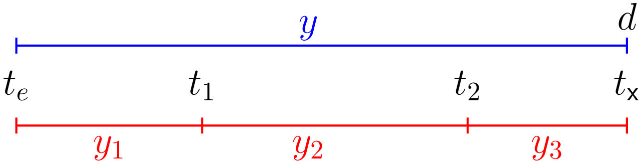
log-Likelihood

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

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

$+ 0 \log(\lambda) - \lambda y_2$

$+ d \log(\lambda) - \lambda y_3$



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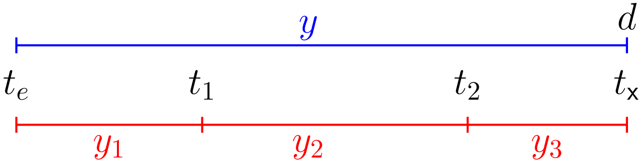
$\times \mathrm{P}(d \text{ at } t_x \mid \text{entry } t_2)$	$+ d\log(\lambda_3) - \lambda_3 y_3$

$\Rightarrow$ allows different rates (λ_i) in each interval



Probability	log-Likelihood
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— allows different rates (λ_i) in each interval

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)
 lex.id tfl lex.dur lex.Cst lex.Xst inst   time status age sex ph.ecog ph.karno
      1   0   10.05   Alive    Dead    3 10.053      2  74   M       1       90
      2   0   14.95   Alive    Dead    3 14.949      2  68   M       0       90
      3   0   33.18   Alive   Alive    3 33.183      1  56   M       0       90
      4   0    6.90   Alive    Dead    5  6.899      2  57   M       1       90
      5   0   29.01   Alive    Dead    1 29.010      2  60   M       0      100
      6   0   33.58   Alive   Alive   12 33.577      1  74   M       1       50
 pat.karno meal.cal wt.loss
       100     1175      NA
        90     1225      15
        90       NA      15
        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 date of lung cancer. Defines a **timescale** with name `tfl`.
- `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=`.

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

`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=`

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 date of lung cancer. Defines a **timescale** with name `tfl`.
- `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=`

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`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?

Lexis object: Overview of follow-up

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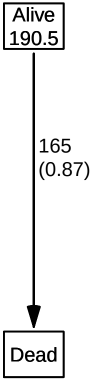
> summary(L1)

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 = 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 0.856
age       1.017 0.999 1.036     1.016 0.998 1.034
```

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

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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
```

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]
```

```
 lex.id tfl lex.dur lex.Cst lex.Xst inst  time status age sex
     10   0    5.45   Alive    Dead    7 5.454      2  61   M
```

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

```
 lex.id tfl lex.dur lex.Cst lex.Xst inst  time status age sex
     10   0    1.00   Alive   Alive    7 5.454      2  61   M
     10   1    1.00   Alive   Alive    7 5.454      2  61   M
     10   2    1.00   Alive   Alive    7 5.454      2  61   M
     10   3    1.00   Alive   Alive    7 5.454      2  61   M
     10   4    1.00   Alive   Alive    7 5.454      2  61   M
     10   5    0.45   Alive    Dead    7 5.454      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 = 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?

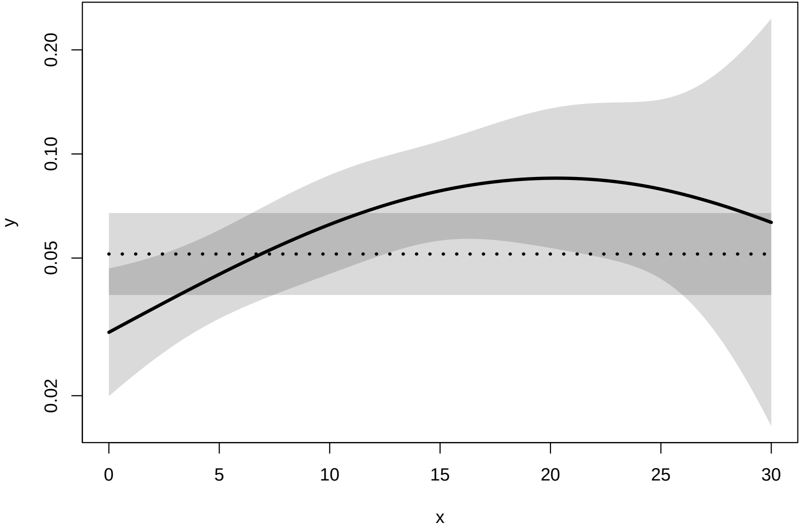
ps is a model for the hazard so we can predict the value of it at defined values for the covariates in the model:

```
> 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

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

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

Survival function and hazard function

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```
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```
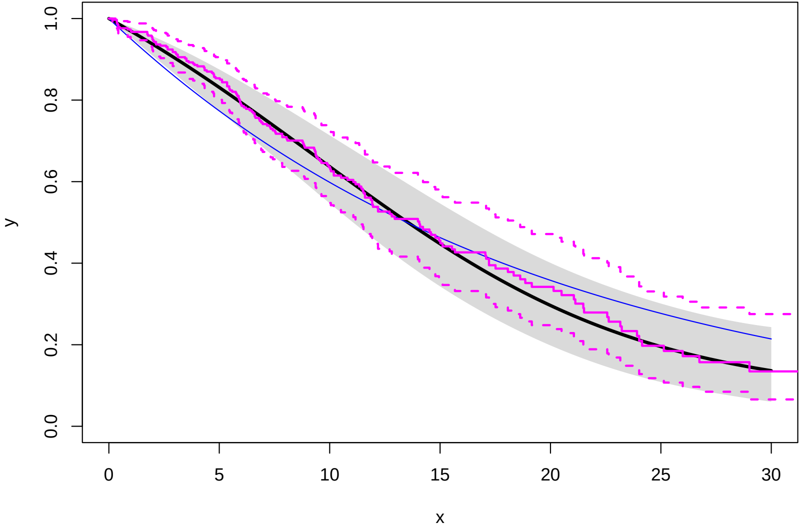
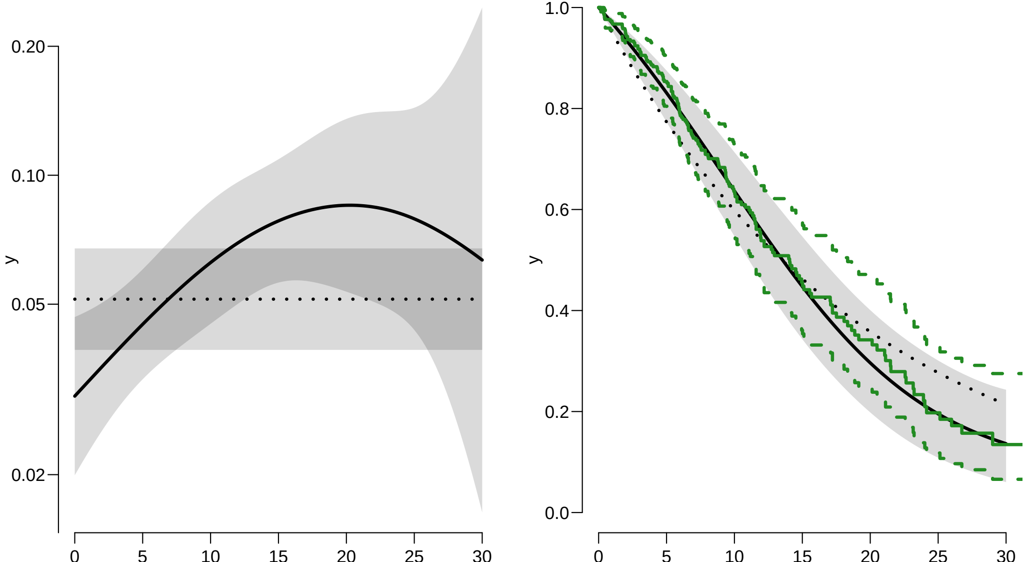

Survival functions



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

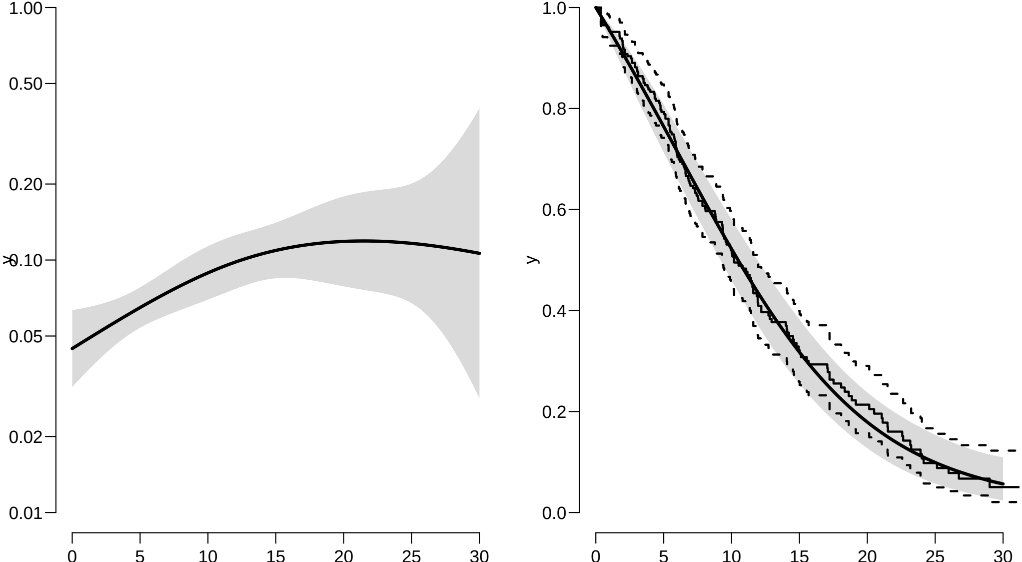


K-M estimator and smooth Poisson model

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

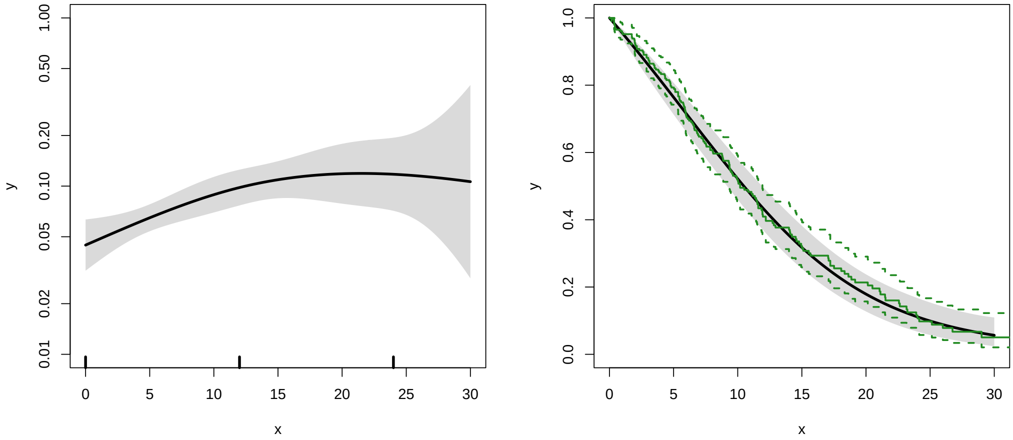


K-M estimator and smooth Poisson model

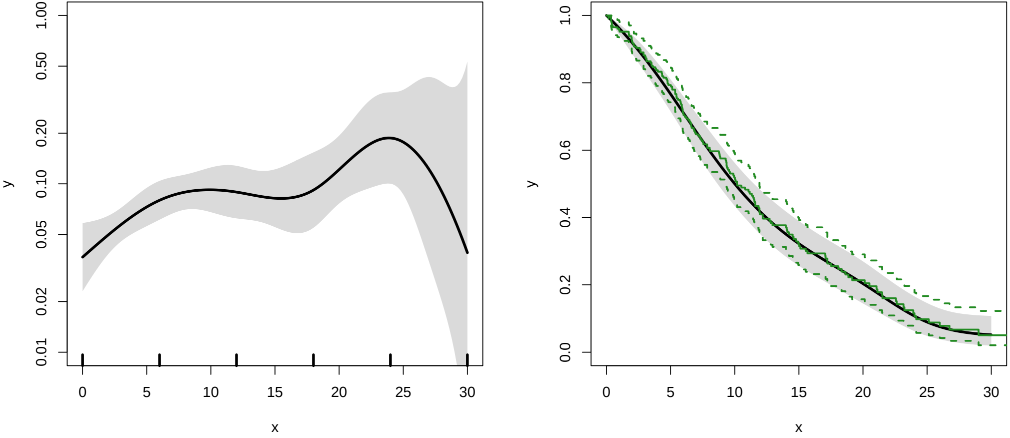
We can explore how the tightness of the knots in the smooth model influence the underlying hazard and the resulting survival function:

```
> 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



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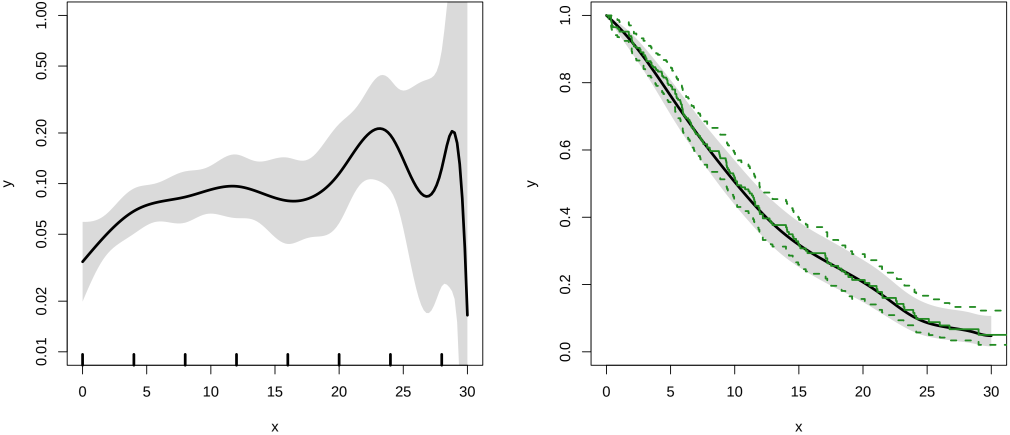
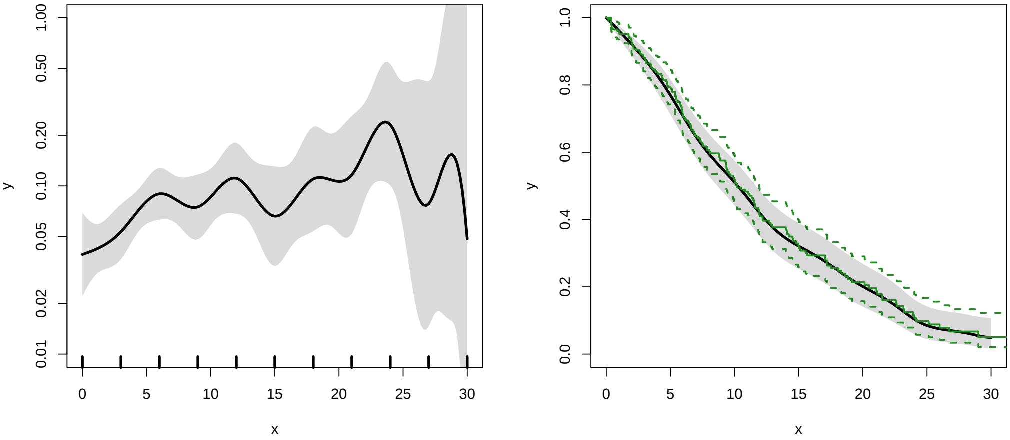
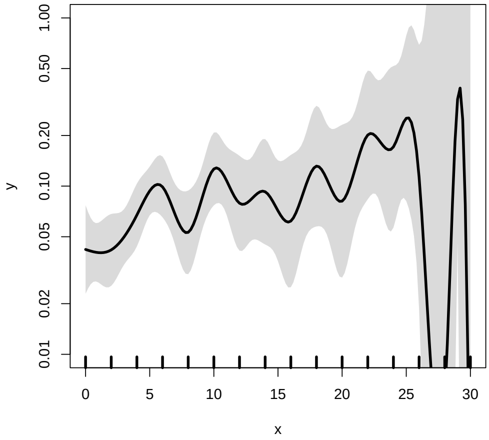
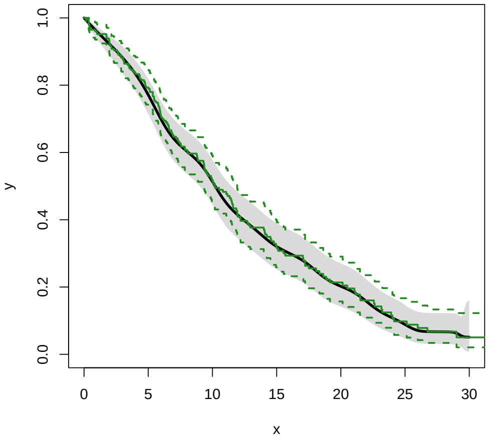


K-M estimator and smooth Poisson model



K-M estimator and smooth Poisson model





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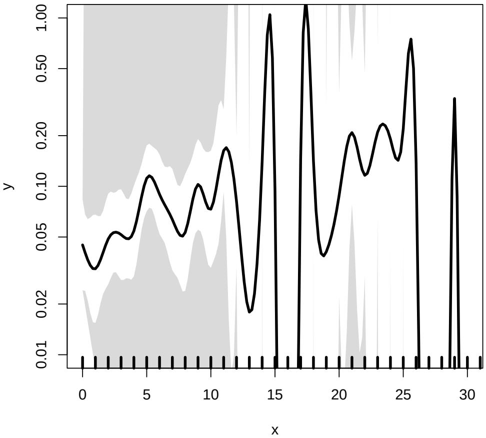

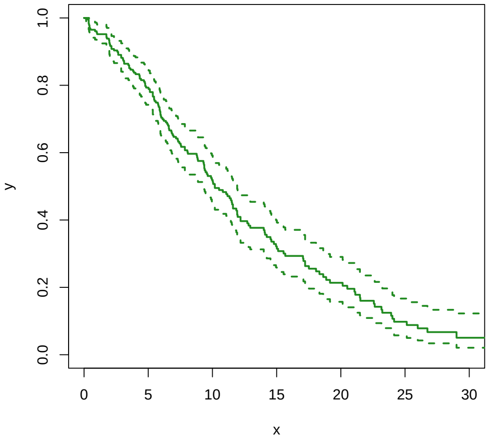

Survival analysis summary

- 1 to 1 correspondence between
  - hazard function and starting point
  - survival function
- K-M and Cox use a very detailed baseline hazard (omits it)
- Smooth parametric hazard function more credible

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  - `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)
```

Competing risks

estimation

Multistate models:
Occurrence rates, cumulative risks, competing risks,
state probabilities with multiple states and time scales using **R** and `Epi::Lexis`
Baker HDI, 22-23 February 2023

```
> 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 Ins

```
> Ldm <- sortLexis(Ldm)
> Cdm <- cutLexis(Ldm,
+                  cut = Ldm$doins,
+            timescale = "per",
+            new.state = "Ins")
> summary(Cdm)
```

```
Transitions:
     To
From    DM Ins Dead  Records:  Events: Risk time:  Persons:
  DM  1258 330  398      1986      728     9015.5      1986
  Ins    0 263   80       343       80     1726.8       343
  Sum 1258 593  478      2329      808    10742.3      1999
```

Cut follow-up at the date of `Ins`, `doins`

```
> subset(Ldm, lex.id %in% c(2,3,4,34))[,c(1:7,13)]
```

```
 lex.id    per   age tfd lex.dur lex.Cst lex.Xst  doins
      2 2005.6 61.52   0    4.35      DM      DM     NA
      3 2007.9 51.10   0    2.11      DM      DM     NA
      4 2007.0 54.61   0    3.03      DM      DM 2008.0
     34 2002.8 69.65   0    4.01      DM    Dead 2002.9
```

```
> subset(Cdm, lex.id %in% c(2,3,4,34))[,c(1:7,13)]
```

```
 lex.id    per   age  tfd lex.dur lex.Cst lex.Xst  doins
      2 2005.6 61.52 0.00    4.35      DM      DM     NA
      3 2007.9 51.10 0.00    2.11      DM      DM     NA
      4 2007.0 54.61 0.00    1.06      DM     Ins 2008.0
      4 2008.0 55.67 1.06    1.97     Ins     Ins 2008.0
     34 2002.8 69.65 0.00    0.07      DM     Ins 2002.9
     34 2002.9 69.72 0.07    3.94     Ins    Dead 2002.9
```

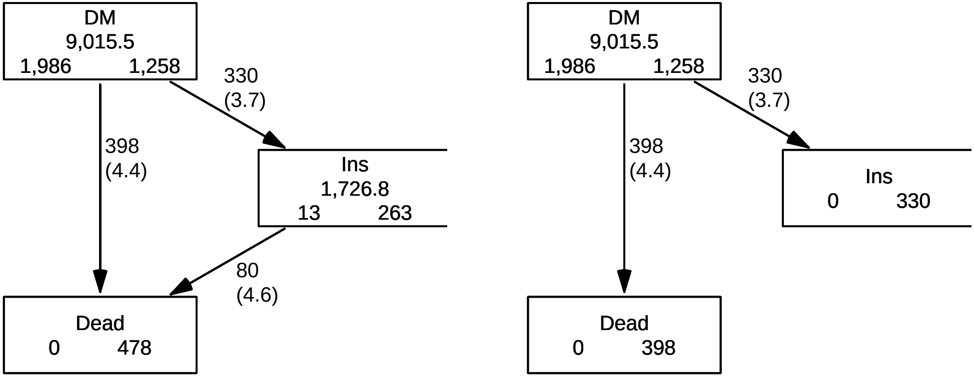
Restrict to those alive in DM

```
> Adm <- subset(Cdm, lex.Cst == "DM")
> summary(Adm)

Transitions:
     To
From   DM Ins Dead  Records:  Events: Risk time:  Persons:
  DM 1258 330  398      1986      728     9015.5      1986

> 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 `Ins` 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: the probability of being in each of the states DM, `Ins` and `Dead`
  - depends on two rates: DM → `Ins` and DM → `Dead`

Survival function?

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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 ties together records belonging to the same person
4. the initial state (DM) must be the first level of the factor `lex.Xst`

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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"   "Ins"  "Dead"

> m3 <- survfit(Surv(tfd, tfd + lex.dur, lex.Xst) ~ 1,
+                  id = lex.id,
+                data = Adm)
> # names(m3)
> m3$states

[1] "(s0)" "Ins"  "Dead"

> head(cbind(time = m3$time, m3$pstate))

          time
[1,] 0.0054757 0.99950 0.0000000 0.00050352
[2,] 0.0082136 0.99748 0.0010070 0.00151057
[3,] 0.0109514 0.99547 0.0025184 0.00201435
[4,] 0.0136893 0.99396 0.0040297 0.00201435
[5,] 0.0164271 0.99295 0.0050373 0.00201435
[6,] 0.0191650 0.98942 0.0085637 0.00201435
```

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

Survival function and cumulative risks—formulae

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

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

Survival function and cumulative risks—formulae

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

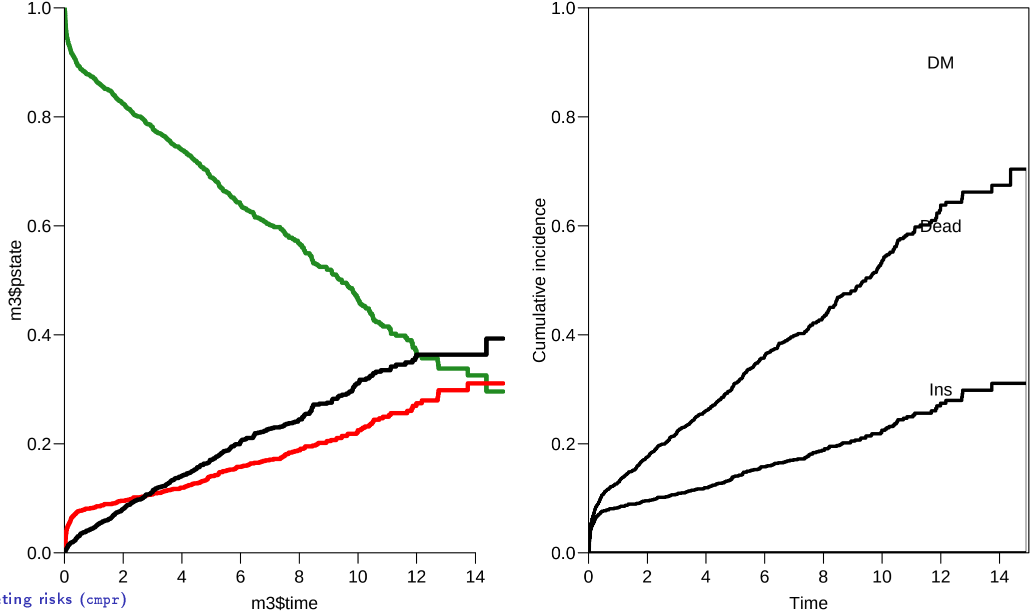
$$
S(t) + R_{\texttt{Ins}}(t) + R_{\texttt{Dead}}(t) = 1, \quad \forall t
$$

Survival function and cumulative risks

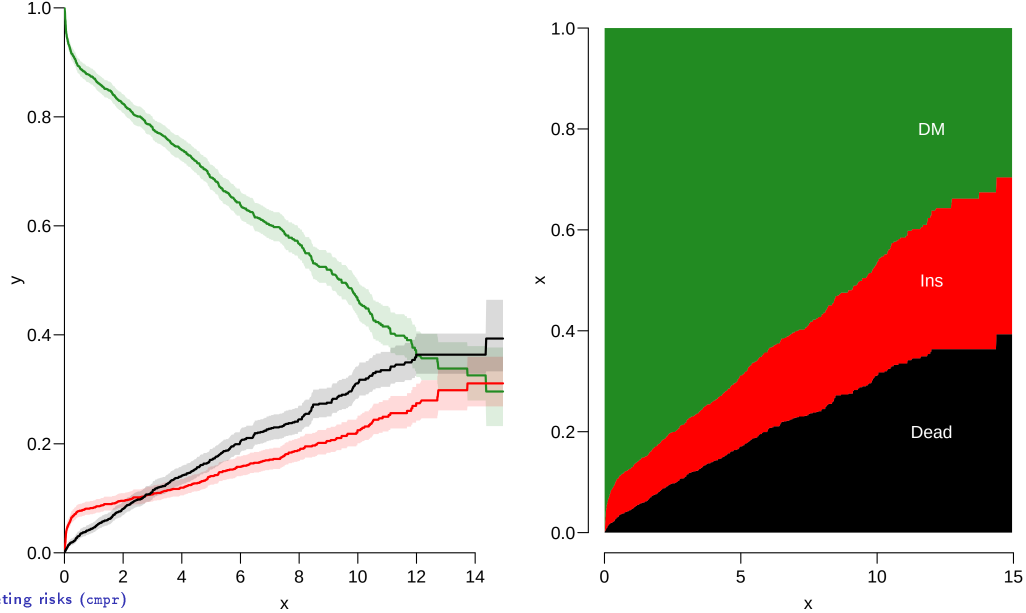
```
> par( mfrow=c(1,2) )
> matplot(m3$time, m3$pstate,
+         type="s", lty=1, lwd=4,
+         col=c("ForestGreen","red","black"),
+         xlim=c(0,15), xaxs="i",
+         ylim=c(0,1), yaxs="i" )
> stackedCIF(m3, lwd=3, xlim=c(0,15), xaxs="i", yaxs="i" )
> text(rep(12,3), c(0.9,0.3,0.6), levels(Cdm))
> 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 = 2,
+          col = clr <- c("ForestGreen","red","black"),
+          xlim=c(0,15), xaxs="i",
+          ylim = c(0,1), yaxs = "i")
> mat2pol(m3$pstate, perm = 3:1, x = m3$time, col = clr[3:1])
> text(rep(12, 3), c(0.8, 0.5, 0.2), levels(Cdm), col = "white")
```

Survival and cumulative risk functions



Survival and cumulative risk functions



Survival function and cumulative risks—don't

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&\neq \int_0^t \lambda(u) \exp\left(-\int_0^u \lambda(s)\,\mathrm{d}s\right)\mathrm{d}u \\
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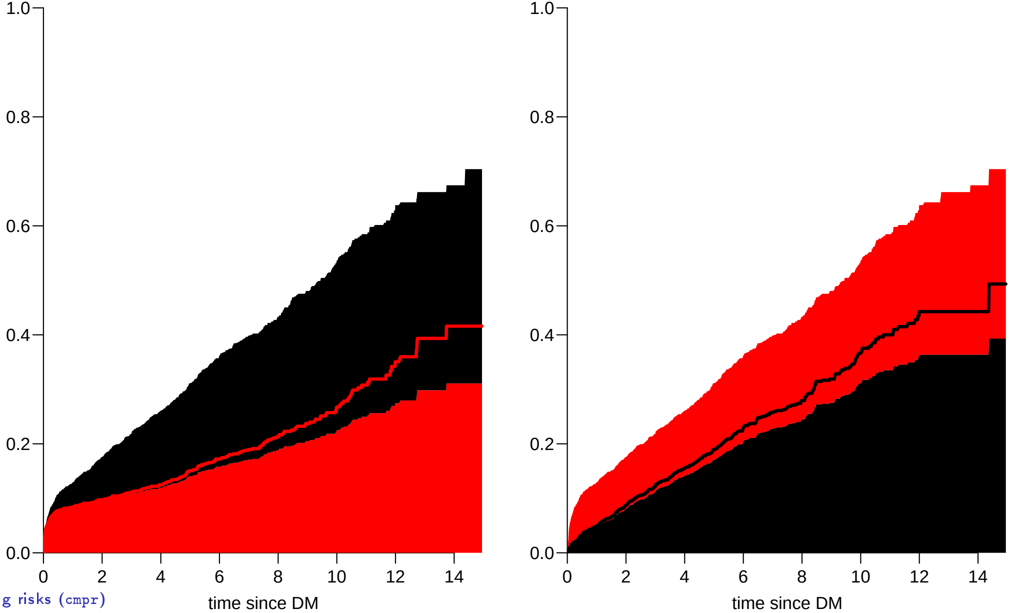
\end{aligned}$$

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

Survival function and cumulative risks—don't

```
> m2 <- survfit(Surv(tfd,
+                    tfd + lex.dur,
+                    lex.Xst == "Ins" ) ~ 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.
- These models have no common parameters (effects of time or other covariates are not constrained to be the same).
- … not for technical or statistical reasons, but for substantial reasons:

  It is unlikely that rates of different types of event (insulin initiation and death, say) depend on time in the same way.

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  it is unlikely that rates of different types of event (Insulin 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 Ins Dead  Records:  Events: Risk time:  Persons:
  DM 1258 330  398      1986       728     9015.5      1986

> summary(Sdm)

Transitions:
     To
From    DM Ins Dead  Records:  Events: Risk time:  Persons:
  DM 90419 330  398     91147       728     9015.5      1986
```

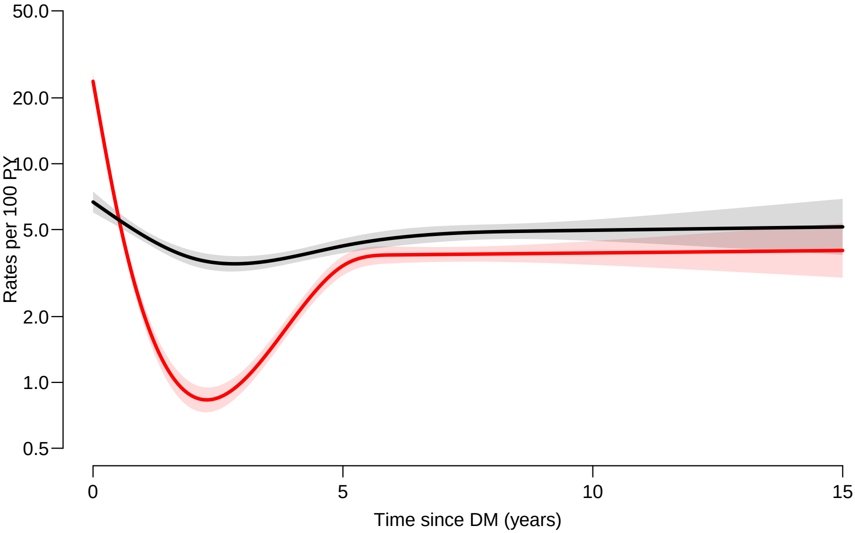
Cause-specific rates

```
> round(cbind(
+ with(subset(Sdm, lex.Xst == "Ins" ), quantile(tfd + lex.dur, 0:4/4)),
+ with(subset(Sdm, lex.Xst == "Dead"), quantile(tfd + lex.dur, 0:4/4))), 2)

      [,1]  [,2]
0%    0.01  0.01
25%   0.07  1.15
50%   1.07  3.01
75%   5.19  5.69
100% 13.74 14.38

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

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

> 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
```

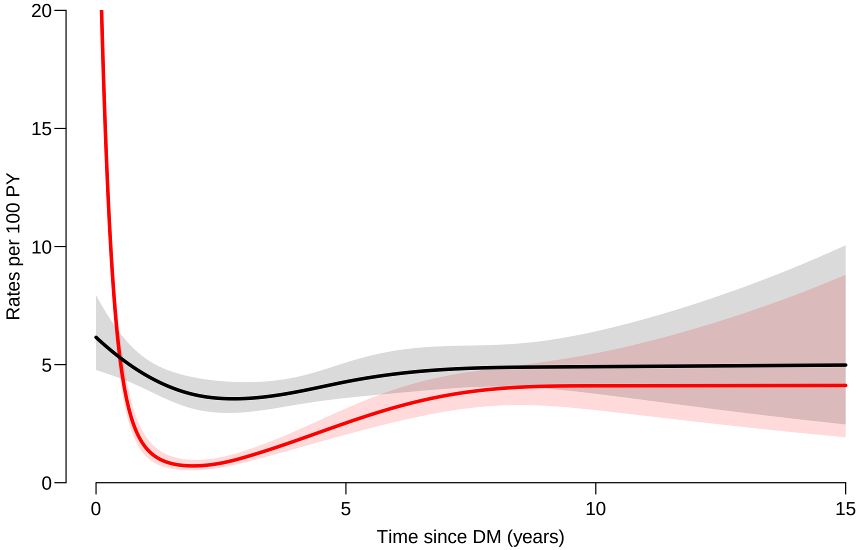
Cause-specific rates

```
> int <- 0.01
> nd <- data.frame(tfd = seq(0, 15, int))
> l.glm <- ci.pred( Ins.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,
+          xlab = "Time since DM (years)",
+          ylab = "Rates per 100 PY")
```

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.
- In R, a curve of the function $y(t)$ is a set of two vectors one vector of ts and one vector $y = y(t)$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` on this gives the predicted rates.
- Then use the formuale with all the integrals to get the state probabilities.

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- Using `ci.pred` on this gives the predicted rates
- Then use the formuale with all the integrals to get the state probabilities.

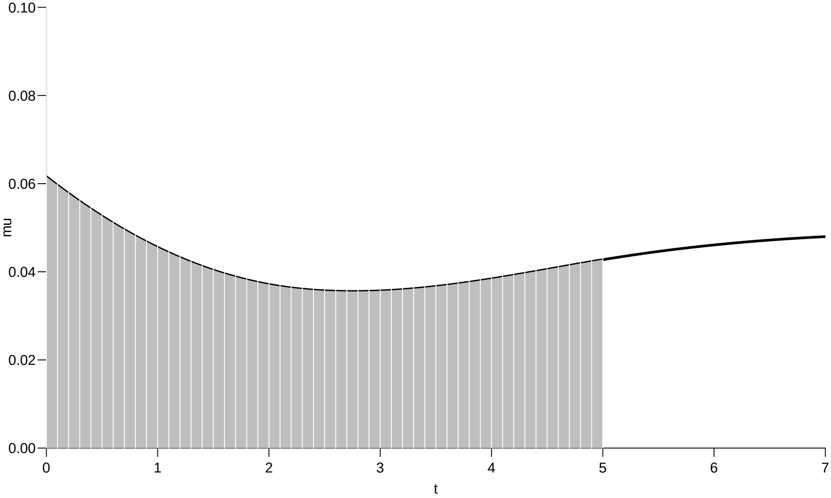
Integrals with R

```
> 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 0.061567
2 0.01 0.061372
3 0.02 0.061177
4 0.03 0.060983
5 0.04 0.060790
6 0.05 0.060597

> 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 0.061470
3 0.01 0.061275
4 0.01 0.061080
5 0.01 0.060887
6 0.01 0.060694
```

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 0.0000000
2 0.01 0.0006147
3 0.02 0.0012274
4 0.03 0.0018383
5 0.04 0.0024471
6 0.05 0.0030541
```

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.

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

Simulation of cumulative risks: `ci.Crisk`

1. a random vector from the multivariate normal distribution with
   - mean equal to the parameters of the model
   - 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. derive state probabilities at these times by numerical integration
4. repeat to obtain, say, 1000 sets of state probabilities at these times
5. derive confidence intervals for the state probabilities as the 2.5 and 97.5 percentiles of the state probabilities at each time

This machinery is implemented in the function `ci.Crisk` in Epi

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2. use this to generate a simulated set of rates $(\lambda(t), \mu(t))$, evaluated a closely spaced times
3. derive state probabilities at these times by numerical integration
4. repeat to obtain, say, 1000 sets of state probabilities at these times
5. derive confidence intervals for the state probabilities as the 2.5 and 97.5 percentiles of the state probabilities at each time

This machinery is implemented in the function `ci.Crisk` in Epi

Simulation of cumulative risks: `ci.Crisk`

1. a random vector from the multivariate normal distribution with
   - mean equal to the parameters of the model,
   - 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. derive state probabilities at these times by numerical integration
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5. derive confidence intervals for the state probabilities as the 2.5 and 97.5 percentiles of the state probabilities at each time

This machinery is implemented in the function `ci.Crisk` in `Epi`

Cumulative risks from parametric models

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

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

```
> str(cR)
```

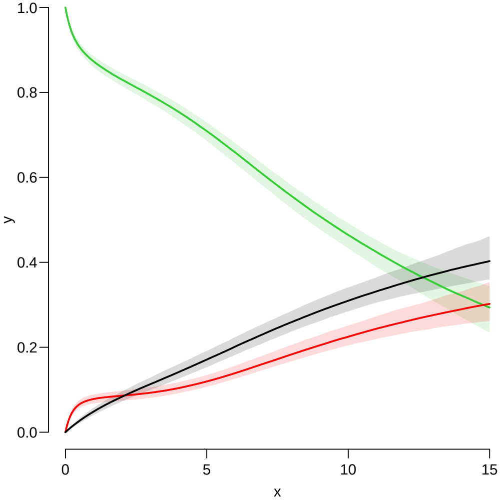
```
List of 4
 $ Crisk: num [1:1501, 1:3, 1:3] 1 0.996 0.993 0.989 0.986 ...
  ..- attr(*, "dimnames")=List of 3
  .. ..$ tfd  : chr [1:1501] "0" "0.01" "0.02" "0.03" ...
  .. ..$ cause: chr [1:3] "Surv" "Ins" "Dead"
  .. ..$      : chr [1:3] "50%" "2.5%" "97.5%"
 $ Srisk: num [1:1501, 1:2, 1:3] 0 0.000618 0.001232 0.001841 0.002447 ...
  ..- attr(*, "dimnames")=List of 3
  .. ..$ tfd  : chr [1:1501] "0" "0.01" "0.02" "0.03" ...
  .. ..$ cause: chr [1:2] "Dead" "Dead+Ins"
  .. ..$      : chr [1:3] "50%" "2.5%" "97.5%"
 $ Stime: num [1:1501, 1:3, 1:3] 0 0.00998 0.01993 0.02984 0.03972 ...
  ..- attr(*, "dimnames")=List of 3
  .. ..$ tfd  : chr [1:1501] "0" "0.01" "0.02" "0.03" ...
  .. ..$ cause: chr [1:3] "Surv" "Ins" "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)

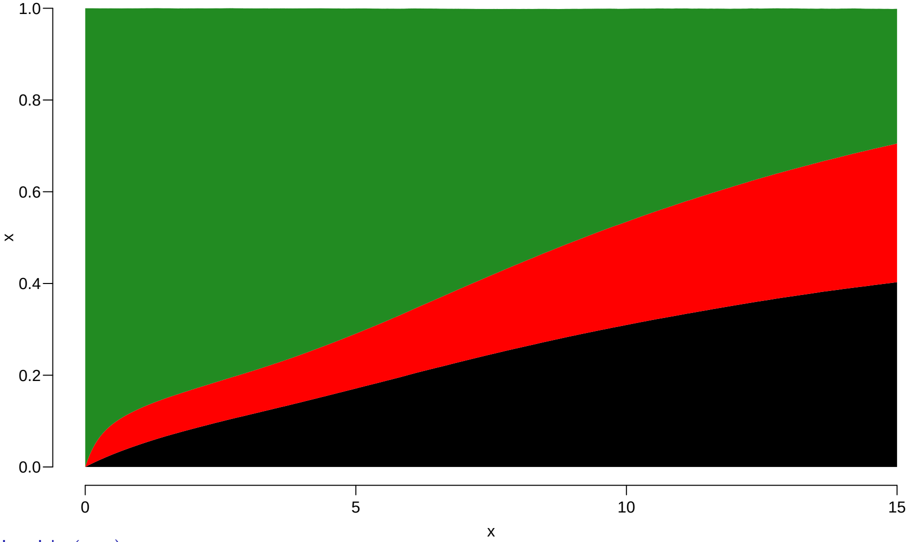
```
> mat2pol(cR$Crisk[,3:1,1], col = c("forestgreen","red","black")[3:1])
```

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

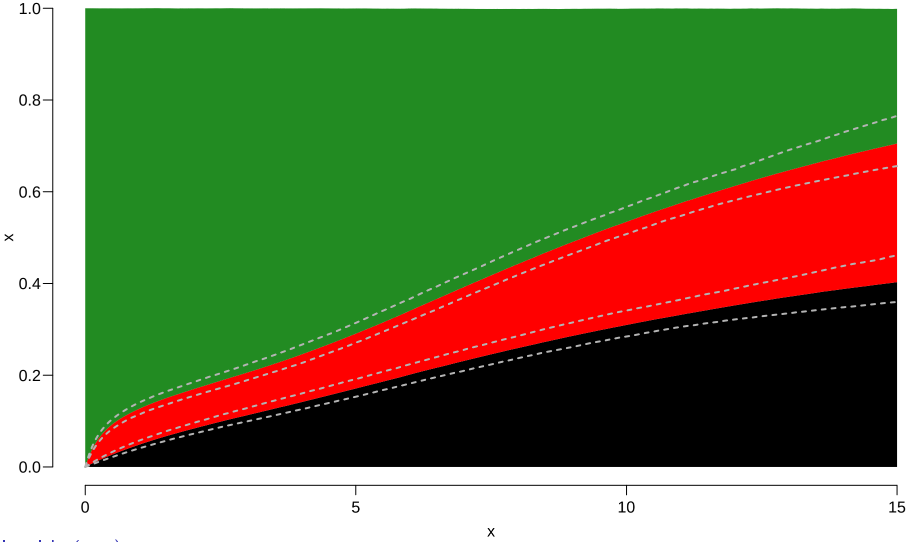
The component `Srisk` has the confidence limits of the stacked probabilities:

```
> mat2pol(cR$Crisk[,3:1,1], col = c("forestgreen","red","black")[3:1])
> matlines(as.numeric(dimnames(cR$Srisk)[[1]]),
+          cbind(cR$Srisk[,"Dead"    ,2:3],
+                cR$Srisk[,"Dead+Ins",2:3]),
+          lty = "32", 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 Ins
- expected years lost to death without Ins
- expected years after Ins, including years dead after Ins

Not all 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)

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Not all 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 Ins during the first 5, 10 and 15 years:

```
> str(cR$Stime)
 num [1:1501, 1:3, 1:3] 0 0.00998 0.01993 0.02984 0.03972 ...
 - attr(*, "dimnames")=List of 3
  ..$ tfd  : chr [1:1501] "0" "0.01" "0.02" "0.03" ...
  ..$ cause: chr [1:3] "Surv" "Ins" "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  4.1  4.0   4.2
  10 7.0  6.8   7.2
  15 8.9  8.5   9.2
```

Multistate model

simulation

Multistate models:
Occurrence rates, cumulative risks, competing risks,
state probabilities with multiple states and time scales using **R** and `Epi::Lexis`
Baker HDI, 22-23 February 2023

BAckground: Steno 2 trial

- Clinical trial for diabetes ptt. with kidney disease (micro-albuminuria)

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  - Intensified multifactorial treatment
- 1993–2001
- follow-up till 2018

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  - Conventional treatment
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Steno 2 trial: goal

- Is there a treatment effect on:
  - CVD mortality
  - non-CVD mortality
- Does the treatment effect depend on
- Quantification of treatment effect

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  - Rate ratios
  - Life times
  - Changes in clinical parameters

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  - CVD mortality
  - non-CVD mortality
- Does the treatment effect depend on:
  - Albuminuria state
- Quantification of treatment effect:
  - Rate-ratios
  - Life-times
  - Changes in clinical parameters

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  - CVD mortality
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  - Albuminuria state
- Quantification of treatment effect:
  - 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?

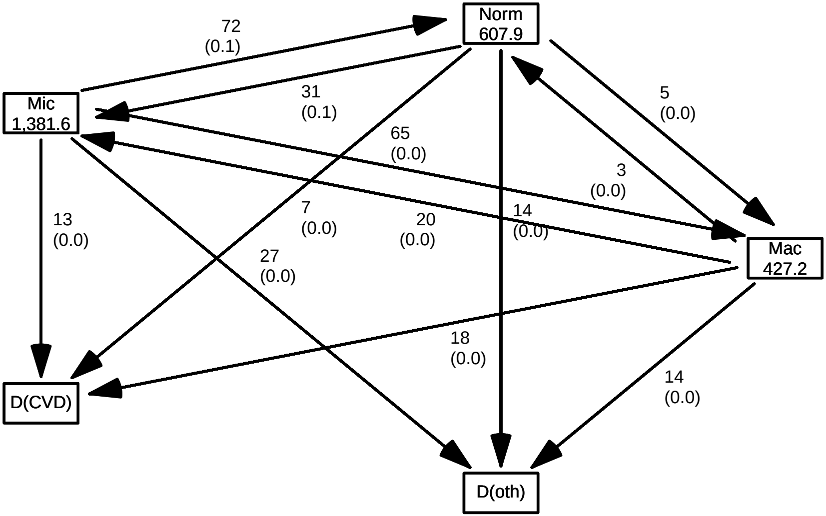
Albuminuria status as states

```
> 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
     70 1999.49    2.67     Mac    Norm
     86 2001.76   12.82    Norm     Mac
    130 2000.91    1.88     Mac    Norm
    131 1997.76    4.24    Norm     Mac
    136 1997.21    0.47     Mac    Norm
    136 1997.69    4.24    Norm     Mac
    171 1996.39    5.34    Norm     Mac
    175 2004.58    9.88    Norm     Mac
```

—and what will you do about it?

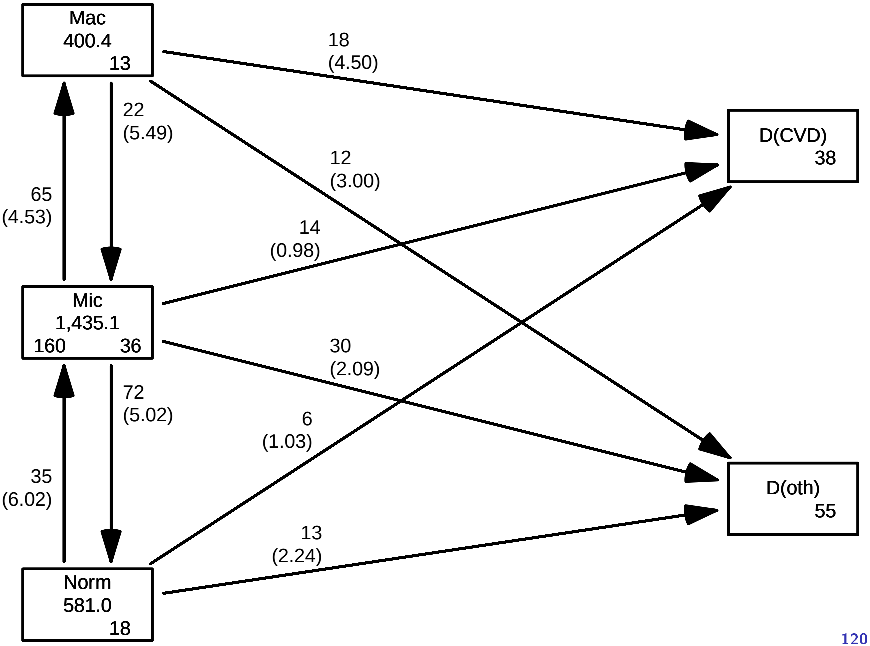
How to fix things

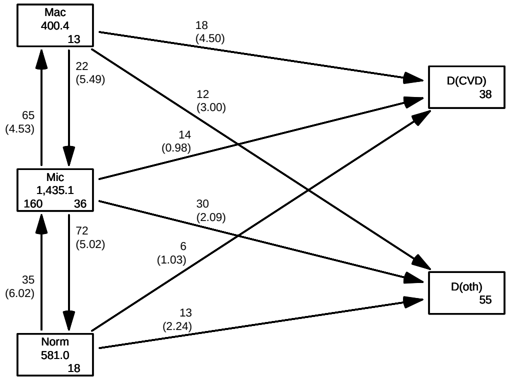
```
> set.seed(1952)
> xcut <- transform(jump,
+                   cut = per + lex.dur * runif(per, 0.1, 0.9),
+             new.state = "Mic")
> xcut <- select(xcut, c(lex.id, cut, new.state))
> L4 <- rcutLexis(L3, xcut)
> L4 <- Relevel(L4, c("Norm","Mic","Mac","D(CVD)","D(oth)"))
> summary(L4)

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)
12
(3.00)
65
(4.53)
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` (or `splitMulti` from `popEpi`)
- Compare the `Lexis` objects

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- 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
```

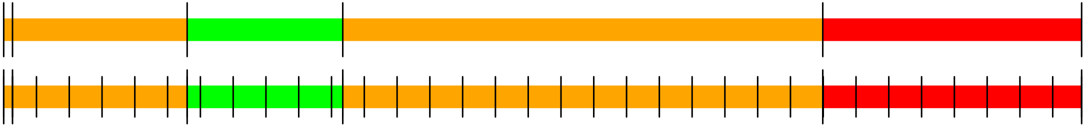
How the split works:

```
> subset(L4, lex.id == 96)[,1:7]

 lex.id      per   age  tfi lex.dur lex.Cst lex.Xst
     96 1993.65 51.53 0.00    0.45     Mic    Norm
     96 1994.10 51.99 0.45    2.58    Norm    Norm
     96 1996.68 54.57 3.03    1.90    Norm    Norm
     96 1998.59 56.47 4.94    2.90    Norm  D(CVD)

> s4 <- subset(S4, lex.id == 96)[,1:7]
> s4[c(1:4,NA,nrow(s4)+(-3:0)),]

 lex.id      per   age  tfi lex.dur lex.Cst lex.Xst
     96 1993.65 51.53 0.00    0.45     Mic    Norm
     96 1994.10 51.99 0.45    0.05    Norm    Norm
     96 1994.15 52.03 0.50    0.50    Norm    Norm
     96 1994.65 52.53 1.00    0.50    Norm    Norm
     NA      NA    NA   NA      NA    <NA>    <NA>
     96 1999.65 57.53 6.00    0.50    Norm    Norm
     96 2000.15 58.03 6.50    0.50    Norm    Norm
     96 2000.65 58.53 7.00    0.50    Norm    Norm
     96 2001.15 59.03 7.50    0.33    Norm  D(CVD)
```

```
> subset(L4, lex.id == 159)[,1:7]
 lex.id     per   age   tfi lex.dur lex.Cst lex.Xst
    159 1994.02 67.50  0.00    0.13     Mic     Mic
    159 1994.16 67.63  0.13    2.66     Mic    Norm
    159 1996.82 70.29  2.80    2.37    Norm     Mic
    159 1999.20 72.67  5.17    7.32     Mic     Mac
    159 2006.52 79.99 12.49    3.95     Mac  D(CVD)
```

```
> 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
    159 1994.02 67.50  0.00    0.13     Mic     Mic
    159 1994.16 67.63  0.13    0.37     Mic     Mic
     NA      NA    NA    NA      NA    <NA>    <NA>
    159 1996.02 69.50  2.00    0.50     Mic     Mic
    159 1996.52 70.00  2.50    0.30     Mic    Norm
     NA      NA    NA    NA      NA    <NA>    <NA>
    159 1998.52 72.00  4.50    0.50    Norm    Norm
    159 1999.02 72.50  5.00    0.17    Norm     Mic
     NA      NA    NA    NA      NA    <NA>    <NA>
    159 2005.52 79.00 11.50    0.50     Mic     Mic
    159 2006.02 79.50 12.00    0.49     Mic     Mac
     NA      NA    NA    NA      NA    <NA>    <NA>
    159 2009.52 83.00 15.50    0.50     Mac     Mac
    159 2010.02 83.50 16.00    0.44     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
- values of covariates differ between intervals
- each interval contributes 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

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  `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.
-1.368e-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 simplifies things substantially:

```
> 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

> summary(coef(mp) - coef(mL))

      Min.    1st Qu.     Median       Mean    3rd Qu.       Max.
-6.839e-13  7.883e-15  2.887e-14  1.625e-13  2.364e-13  1.368e-12
```

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)
```

```
NOTE:
Multiple transitions *from* state ' Mac', 'Mic', 'Norm ' - are you sure?
The analysis requested is effectively merging outcome states.
You may want analyses using a *stacked* dataset - see ?stack.Lexis
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->D(oth)
Mac->D(oth)
```

Describe the model(s) in mX (look at the figure with the boxes)

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

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