Practice in analysis of multistate models using Epi::Lexis

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http://BendixCarstensen/AdvCoh/courses/Frias-2016

Introducing R

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The best way to learn R

- The best way to learn **R** is to use it!
- This is a very short introduction before you sit down in front of a computer.
- **R** is a little different from other packages for statistical analysis.
- These differences make **R** very powerful, but for a new user they can sometimes be confusing.
- Our first job is to help you up the initial learning curve so that you can be comfortable with R.

Nothing is lost or hidden

- Statistical software provides "canned" procedures to address common statistical problems.
- Canned procedures are useful for routine analysis, but they are also limiting.
  - You can only do what the programmer lets you do.
- In R, the results of statistical calculations are always accessible.
  - You can use them for further calculations.
  - You can always see how the calculations were done.

R Packages

- The capabilities of **R** can be extended using "packages".
- Distributed over the Internet *via* **CRAN**:
(the **C**omprehensive **R** **A**rchive **N**etwork) and can be downloaded directly from an **R** session.
- There is an **R** package developed during the annual course on "Statistical Practice in Epidemiology using **R**, called "Epi".
- Contains special functions for epidemiologists and some data sets that .
- There are 5,825 other user contributed packages on CRAN.

Objects and functions

R allows you to build powerful procedures from simple building blocks. These building blocks are **objects** and **functions**.

- All data in **R** is represented by **objects**, for example:
  - A dataset (called data frame in R)
  - A vector of numbers
  - The result of fitting a model to data
- You, the user, call **functions**
- Functions act on objects to create **new objects**:
- Using `glm` on a dataframe (an object) produces a fitted model (another object).

Because all is functions...

- You will always (almost) use parentheses:
```
> res <- FUN( x, y )
```
- ...which is pronounced
- `res` **gets** ("<-") `FUN` **of** `x,y` ("(x,y)")

Vectors

One of the simplest objects in **R** is a sequence of numbers, called a **vector**.

You can create a vector in **R** with the collection (`c`) function:

```
> c(1,3,2)
[1] 1 3 2
```

You can save the results of any calculation using the left arrow:

```
> x <- c(1,3,2)
> x
[1] 1 3 2
```


The workspace

- Every time you use `<-`, you create a new object in the **workspace** (or overwrite an old one).
- A list of objects in the workspace can be seen with the `objects` function (synonym: `ls()`):
```
> objects()
[1] "a" "aa" "acz2" "alpha" "b"
[6] "bar" "bb" "bdendo" "beta" "cc"
[11] "Col"
```
- In `Epi` is a function `lls()` that gives a bit more information on the objects.
- The workspace is held entirely in (volatile) computer memory and will be lost at the end of the session unless you explicitly save it.

Working Directory

Every **R** session has a **current working directory**, which is the location on the hard disk where files are saved, and the default location from which files are read into R.

- `getwd()` Prints the current working directory
- `setwd("c:/Users/Martyn/Project")` sets the current working directory.
- You may also use a Graphical User Interface (GUI) to change directory.

Ending an R session

- To end an **R** session, call the `quit()` function
  - Every time you want to do something in R, you call a function.
- You will be asked "Save workspace image?"

  Yes saves the workspace to the file ".RData" in your current working directory. It will be automatically loaded into **R** the next time you start an **R** session.

  No does not save the workspace.

  Cancel continues the current **R** session without saving anything.
- It is recommended you just say "No".

Always start with a clean workspace

Keeping objects in your workspace from one session to another can be dangerous:

- You forget how they were made.
- You cannot easily recreate them if your data changes.
- They may not even be from the same project

It is almost always best to start with an empty workspace and use a script file to create the objects you need from scratch.

Rectangular Data

Rectangular data sets are common to most statistical packages

"id"	"visit"	"time"	"status"
1	1	0.0	0
1	2	1.5	0
2	1	0.0	0
2	2	1.1	0
2	3	2.3	1

Columns represent variables.
Rows represent individual records.

The world is not a rectangle!

- Most statistical packages used by epidemiologists assume that **all data** can be represented as a rectangular data set.
- R allows a much richer set of data structures, represented by *objects* of different *classes*.
- Rectangular data sets are just one type of object that may be in your workspace. This class of object is called a *data frame*.

Data Frames

Each column of a data frame is a variable.

Variables may be of different types:

- **vectors:**
  - **numeric:** `c(1,2,3)`
  - **character:** `c("John","Paul","George","Ringo")`
  - **logical:** `c(FALSE,FALSE,TRUE)`
- **factors:** `factor(c("low","medium","high","low","low"))`

Building your own data frame

Data frames can be constructed from a list of vectors

```
> mydata <- data.frame(x=c(3,6,7),f=c("a","b","a"))
> mydata
  x f
1 3 a
2 6 b
3 7 a
```

Character vectors are automatically converted to factors.

Inspecting data frames

Most data frames are too large to inspect by printing them to the screen, so use:

- `names` returns a vector of variable names.
  - You can use `sort(names(x))` to get them in alphabetical order.
- `head` prints the first few lines, and `tail`...
- `str` prints a brief overview of the **str**ucture of the data frame. Can be used on any object.
- `summary` prints a more comprehensive summary
  - Quantiles for numeric variables
  - Tables for factors

Extracting values from a data frame

Use square brackets to take **subsets** of a data frame

- `mydata[1,2]`. The value in row 1, column 2.
- `mydata[1,]`. The whole of the first row.
- `mydata[,2]`. The whole of the second column.

You can also extract a column from a data frame by name:

- `mydata$age`. The column, or variable, named "age"
- `mydata["age"]`. The same.

Importing data

- R has good facilities for importing data from other applications:
  - `read.dta` for reading Stata datasets.
  - `read.spss` for reading SPSS datasets.
  - `read.xport` and `read.ssd` for reading SAS-datasets.

Reading Text Files

The function `read.table` reads data from a text file and returns a data frame.

- `mydata <- read.table("myfile")`
- `myfile` could be
  - A file in the **current working directory**: `fem.dat`
  - A path to a file: `c:/rex/fem.dat`
  - A URL: `http://BendixCarstensen.com/AdvCoh/Scot-2014/data/bogus.txt`
- Note: `myfile` must be enclosed in quotes.

`write.table` does the opposite.

R uses a forward slash / for file paths. If you want to use backslash, you have to double it:

`c:\\rex\\fem.dat`

Some useful arguments to `read.table`

- `header = TRUE` if first line contains variable names
- `sep=","` if values are comma-separated instead of being space-delimited.
- `as.is = TRUE` to stop strings being converted to factors
- `na.strings = "99"` to denote that 99 means "missing". Default values are:
  - `NA` "Not Available"
  - `NaN` "Not a Number"
- For comma-separated files there is coderead.csv

Reading Binary Data

- **R** can read in data in binary (non-text) format from other statistical systems using the foreign extension package.
- R is an open source project, and relies on the format for binary files to be well-documented.
- Example: SAS `XPORT` format has been adopted as a data exchange standard by the US Food and Drug Administration. SAS CPORT format remains a proprietary format.

Some functions in the foreign package

- `read.dta` for Stata (also `write.dta`)
- `read.xport` for SAS XPORT format (not CPORT)
- `read.epiinfo` for EPIINFO
- `read.mtp` for MiniTab Portable Worksheet
- `read.spss` for SPSS

See the "R Data Import/Export manual" for more details.
`RShowDoc("R-data")`

Accessing databases systems

Microsoft **Access**:

```
> library(RODBC)
> ch <- odbcConnectAccess("../data/theData.mdb")
> bd <- sqlFetch(ch, "aTable" )
```

Microsoft **Excel**:

```
> library( RODBC )
> cnc <- odbcConnectExcel(paste("../theXel.xls",sep=""))
> sht <- sqlFetch( cnc, "theSheet" )
> close( cnc )
```

Other databases

```
> ?odbcConnect
```


Summary - data

- You can use a data frame to organize your variables
- You can extract variables from a data frame using `$`.
- You can extract variables and observation using indecing `[,]`
- You can read in data using
  - `read.table`
  - tailored function from the `foreign` package
  - database interface from the `RODBC` package

Summary - when it goes wrong

When somthing is fishy with an object `obj`, try to find out what you (accidentally) got, by using:

```
> lls()
> str( obj )
> dim( obj )
> length( obj )
> names( obj )
> head( obj )
> class( obj )
> mode( obj )
```


R language

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`http://BendixCarstensen/AdvCoh/courses/Frias-2016` `lang`

Language

- R is a programming language – also on the command line
- (This means that there are *syntax rules*)
- Print an object by typing its name
- Evaluate an expression by entering it on the command line
- Call a function, giving the arguments in parentheses – possibly empty
- Notice `ls` vs. `ls()`

Objects

- The simplest object type is *vector*
- Modes: numeric, integer, character, generic (list)
- Operations are vectorized: you can add entire vectors with `a + b`
- Recycling of objects: If the lengths don't match, the shorter vector is reused

R expressions

```
x <- rnorm(10, mean=20, sd=5)
m <- mean(x)
sum((x - m)^2)
```

- Object names
- Explicit constants
- Arithmetic operators
- Function calls
- Assignment of results to names

Function calls

Lots of things you do with R involve calling functions.
For instance

```
mean(x, na.rm=TRUE)
```

The important parts of this are

- The name of the function
- Arguments: input to the function
- Sometimes, we have named arguments

Function arguments

```
rnorm(10, mean=m, sd=s)
hist(x, main="My histogram")
mean(log(x + 1))
```

Items which may appear as arguments:

- Names of an R objects
- Explicit constants
- Return values from another function call or expression
- Some arguments have their *default values*.
- Use `help(function)` or `args(function)` to see the arguments (and their order and default values) that can be given to any function.

Creating simple functions

```
logit <- function(p) log(p/(1-p))
logit(0.5)

simpsum <-
function(x, dec=5)
{
  # produces mean and SD of a variable
  # default value for dec is 5
round(c(mean=mean(x),sd=sd(x)),dec)
}

x <- rnorm(100)
simpsum(x)
simpsum(x,2)
```


Indexing

- **R** has several useful indexing mechanisms:
- `a[5]` single element
- `a[5:7]` several elements
- `a[-6]` all except the 6th
- `a[c(1,1,2,1,2)]` some elements repeated
- `a[b>200]` logical index
- `a[■well■]` indexing by name

Lists

- Lists are vectors where the elements can have different types
- Functions often return lists
- `lst <- list(A=rnorm(5),B="hello",K=12)`
- Special indexing:
- `lst$A`
- `lst[1:2]` a list with first two first elements (`A` and `B` — NB: single brackets)
- `lst[1]` a list of length 1 which is the first element (codeA — NB: single brackets)
- `lst[[1]]` first element (NB: double brackets) — a vector of length 5.

Classes, generic functions

- R objects have *classes*
- Functions can behave differently depending on the class of an object
- E.g. `summary(x)` or `print(x)` does different things if `x` is numeric, a factor, or a linear model fit

The workspace

- The *global environment* contains R objects created on the command line.
- There is an additional *search path* of loaded packages and attached data frames.
- When you request an object by name, R looks first in the global environment, and if it doesn't find it there, it continues along the search path.
- The search path is maintained by `library()`, `attach()`, and `detach()`
- List the search path by `search()`
- Notice that objects in the global environment may mask objects in packages and attached data frames

Data manipulation and `with`

```
bmi <- with(stud, weight/(height/100)^2)
```

uses variables weight and height in the data frame `stud` (not the variables with the same name in the workspace), but creates the variable `bmi` in the global environment (not in the data frame).

To create a new variable in the data frame, you can use:

```
stud$bmi <- with( stud, weight/(height/100)^2 )
```


Constructors

- Matrices and arrays, constructed by the (surprise) `matrix` and `array` functions.
- You can extract and set names with `names(x)`; for matrices and data frames also `colnames(x)` and `rownames(x)`
- You can also construct a matrix from its columns using `cbind`, whereas joining two matrices with equal no of columns (with the same column names) can be done using `rbind`.

Factors (class variables)

- Factors are used to describe groupings.
- Basically, these are just integer codes plus a set of names for the *levels*
- They have class `"factor"` making them (a) print nicely and (b) maintain consistency
- A factor can also be *ordered* (class `"ordered"`), signifying that there is a natural sort order on the levels
- In model specifications, factors play a fundamental role by indicating that a variable should be treated as a classification rather than as a quantitative variable (similar to a CLASS statement in SAS)

The factor function

- This is typically used when read.table gets it wrong,
- e.g. group codes read as numeric
- or read as factors, but with levels in the wrong order (e.g. c("rare", "medium", "well-done") sorted alphabetically.)
- Notice that there is a slightly confusing use of levels and labels arguments:
  - levels are the value codes *on input*
  - labels are the value codes *on output* (and becomes the levels of the resulting factor)
  - The levels of a factor is shown by the levels() function.

Working with Dates

- Dates are usually read as character or factor variables
- Use the as.Date function to convert them to objects of class "Date"
- If data are not in the default format (yyyy-mm-dd) you need to supply a format specification

```
> as.Date("11/3-1959",format="%d/%m-%Y")
[1] "1959-03-11"
```


Working with Dates

- Computing the differences between Date objects gives an object of class "difftime", which is number of days between the two dates:

```
> as.numeric(as.Date("2007-5-25")-
             as.Date("1959-3-11"),"days")
[1] 17607
```

- In the Epi package is a function that converts dates to calendar years with decimals:

```
> as.Date("1952-07-14")
[1] "1952-07-14"
> cal.yr( as.Date("1952-07-14") )
[1] 1952.533
attr(,"class")
[1] "cal.yr"  "numeric"
```


Basic graphics

The plot() function is a generic function, producing different plots for different types of arguments. For instance, plot(x) produces:

- a plot of observation index against the observations, when x is a numeric variable
- a bar plot of category frequencies, when x is a factor variable
- a time series plot (interconnected observations) when x is a time series
- a set of diagnostic plots, when x is a fitted regression model
- ...

Basic graphics

Similarly, the plot(x,y) produces:

- a scatter plot of x is a numeric variable
- a bar plot of category frequencies, when x is a factor variable

Basic graphics

Examples:

```
x <- c(0,1,2,1,2,2,1,1,3,3)
plot(x)
plot(factor(x))
plot(ts(x))   # ts() defines x as time series
y <- c(0,1,3,1,2,1,0,1,4,3)
plot(x,y)
plot(factor(x),y)
```


Basic graphics

More simple plots:

- hist(x) produces a histogram
- barplot(x) produces a bar plot (useful when x contains counts – often one uses barplot(table(x)))
- boxplot(y x) produces a box plot of y by levels of a (factor) variable x.

Rates and Survival

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http://BendixCarstensen/AdvCoh/courses/Frias-2016 surv-rate

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")

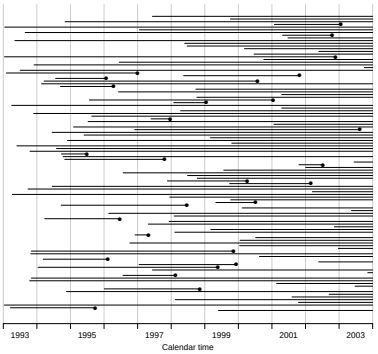
Examples of time-to-event measurements

- 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

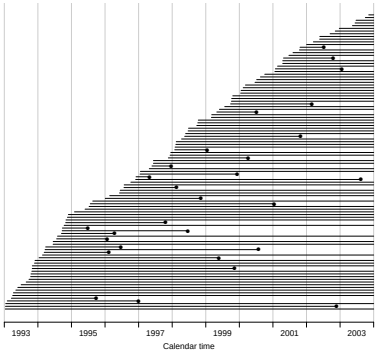
Each blob a death

Study ended at 31 Dec. 2003

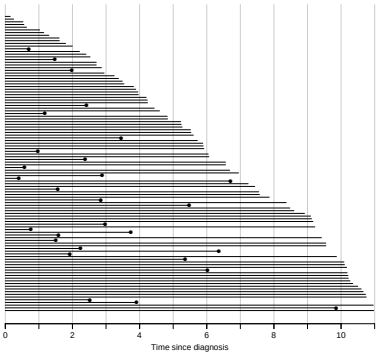


Ordered by date of entry

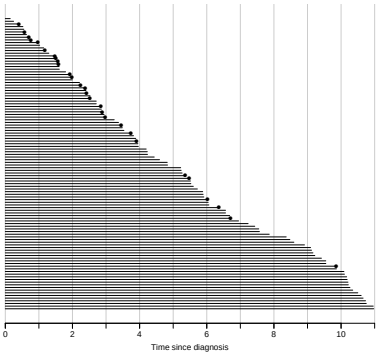
Most likely the order in your database.



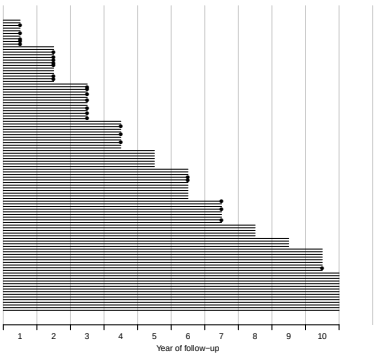
Timescale changed to "Time since diagnosis".



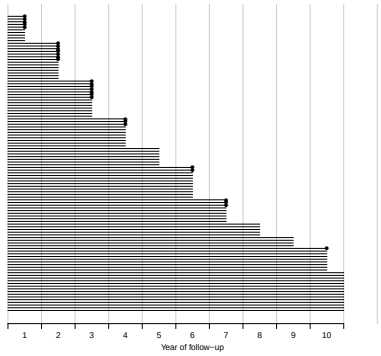
Patients ordered by survival time.



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

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

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

Life-table estimator.

Survival function

Persons enter at time 0:
Date of birth, date of randomization, date of diagnosis.

How long do they survive?
Survival time T — a stochastic variable.

Distribution is characterized by the survival function:

$$\begin{aligned} S(t) &= \mathrm{P}\{\text{survival at least till } t\} \\ &= \mathrm{P}\{T > t\} = 1 - \mathrm{P}\{T \leq t\} = 1 - F(t) \end{aligned}$$

$F(t)$ is the cumulative risk of death before time t.

Intensity or rate

$$\begin{aligned} &\mathrm{P}\{\text{event in } (t, t+h] \mid \text{alive at } t\}/h \\ &= \frac{F(t+h) - F(t)}{S(t) \times h} \\ &= -\frac{S(t+h) - S(t)}{S(t)h} \xrightarrow[h \to 0]{} -\frac{\mathrm{d}\log S(t)}{\mathrm{d}t} \\ &= \lambda(t) \end{aligned}$$

This is the **intensity** or **hazard function** for the distribution. Characterizes the survival distribution as does f or F.

Theoretical counterpart of a **rate**.

Relationships

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

$\Lambda(t) = \int_0^t \lambda(s)\,\mathrm{d}s$ is called the **integrated intensity**. **Not** an intensity, it is dimensionless.

$$\lambda(t) = -\frac{\mathrm{d}\log(S(t))}{\mathrm{d}t} = -\frac{S'(t)}{S(t)} = \frac{F'(t)}{1 - F(t)} = \frac{f(t)}{S(t)}$$

Rate and survival

$$S(t) = \exp\left(-\int_0^t \lambda(s)\,\mathrm{d}s\right) \qquad \lambda(t) = \frac{S'(t)}{S(t)}$$

Survival is a *cumulative* measure, the rate is an *instantaneous* measure.

Note: A cumulative measure requires an origin!

. . . it is always survival **since** some timepoint.

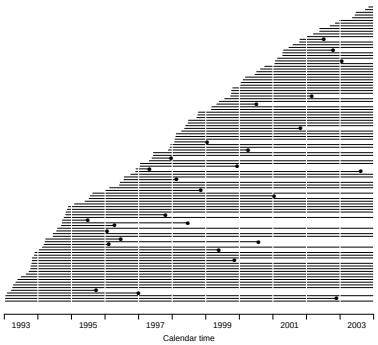
Observed survival and rate

- **Survival studies**: Observation of (right censored) survival time:
  $$X = \min(T, Z), \quad \delta = 1\{X = T\}$$
  — sometimes conditional on $T > t_0$ (left truncation, delayed entry).
- **Epidemiological studies**: Observation of (components of) a rate:
  $$D/Y$$
  D: no. events, Y no of person-years, in a prespecified time-frame.

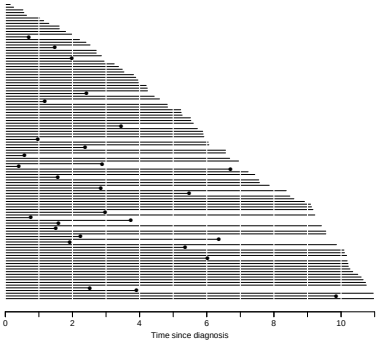
Empirical rates for individuals

- At the *individual* level we introduce the **empirical rate:** (d, y), — number of events ($d \in \{0, 1\}$) during y risk time.
- A person contributes several observations of (d, y), with associated covariate values.
- Empirical rates are **responses** in survival analysis.
- The timescale t is a **covariate** — varies within each individual: t: age, time since diagnosis, calendar time.
- Don't confuse with y — difference between two points on **any** timescale we may choose.

Empirical rates by calendar time.



Empirical rates by time since diagnosis.



Statistical inference: Likelihood

Two things needed:

- **Data** — what did we actually observe
  Follow-up for each person:
  Entry time, exit time, exit status, covariates
- **Model** — how was data generated
  Rates as a function of time:
  Probability machinery that generated data

Likelihood is the probability of observing the data, assuming the model is correct.

Maximum likelihood estimation is choosing parameters of the model that makes the likelihood maximal.

Likelihood from one person

The likelihood from several empirical rates from one individual is a product of conditional probabilities:

$$\begin{aligned}\mathrm{P}\{\text{event at } t_4 | t_0\} &= \mathrm{P}\{\text{survive } (t_0, t_1) | \text{ alive at } t_0\} \times \\ &\quad \mathrm{P}\{\text{survive } (t_1, t_2) | \text{ alive at } t_1\} \times \\ &\quad \mathrm{P}\{\text{survive } (t_2, t_3) | \text{ alive at } t_2\} \times \\ &\quad \mathrm{P}\{\text{event at } t_4 | \text{ alive at } t_3\}\end{aligned}$$

Log-likelihood from one individual is a sum of terms.

Each term refers to one empirical rate (d, y) — $y = t_i - t_{i-1}$ and mostly $d = 0$.

t_i is the timescale (covariate).

Poisson likelihood

The log-likelihood contributions from follow-up of **one** individual:

$$d_t \log\big(\lambda(t)\big) - \lambda(t) y_t, \quad t = t_1, \ldots, t_n$$

is also the log-likelihood from several independent Poisson observations with mean $\lambda(t) y_t$, i.e. log-mean $\log\big(\lambda(t)\big) + \log(y_t)$

Analysis of the rates, (λ) can be based on a Poisson model with log-link applied to empirical rates where:

- d is the response variable.
- $\log(\lambda)$ is modelled by covariates
- $\log(y)$ is the offset variable.

Likelihood for follow-up of many persons

Adding empirical rates over the follow-up of persons:

$$D = \sum d \qquad Y = \sum y \quad \Rightarrow \quad D\log(\lambda) - \lambda Y$$

- Persons are assumed independent
- Contribution from the same person are **conditionally** independent, hence give separate contributions to the log-likelihood.
- Therefore equivalent to likelihood for independent Poisson variates
- No need to correct for dependent observations; the likelihood is a product.

Likelihood

Probability of the data and the parameter:

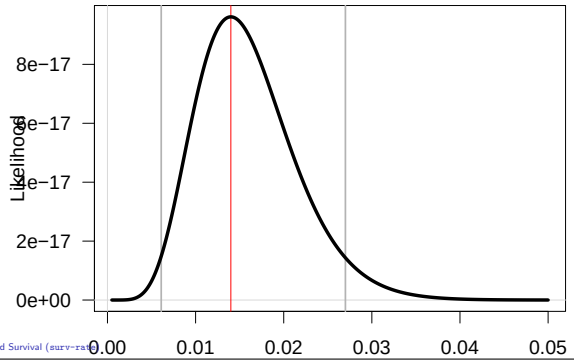
Assuming the rate (intensity) is constant, λ, the probability of observing 7 deaths in the course of 500 person-years:

$$\begin{aligned}\mathrm{P}\{D = 7, Y = 500 | \lambda\} &= \lambda^D \mathrm{e}^{\lambda Y} \times K \\ &= \lambda^7 \mathrm{e}^{\lambda 500} \times K \\ &= L(\lambda | \text{data})\end{aligned}$$

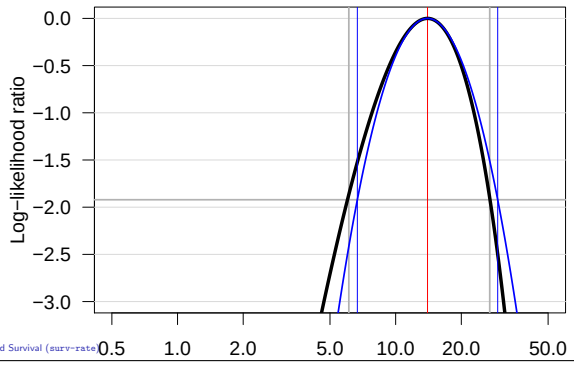
Best guess of λ is where this function is as large as possible.

Confidence interval is where it is not too far from the maximum

Likelihood function



Likelihood function



Confidence interval for a rate

A 95% confidence interval for the log of a rate is:

$$\hat{\theta} \pm 1.96/\sqrt{D} = \log(\lambda) \pm 1.96/\sqrt{D}$$

Take the exponential to get the confidence interval for the rate:

$$\lambda \stackrel{\times}{\div} \underbrace{\exp(1.96/\sqrt{D})}_{\text{error factor,erf}}$$

Example

Suppose we have 17 deaths during 843.6 years of follow-up.

The rate is computed as:

$$\hat{\lambda} = D/Y = 17/843.7 = 0.0201 = 20.1 \text{ per 1000 years}$$

The confidence interval is computed as:

$$\hat{\lambda} \stackrel{\times}{\div} \text{erf} = 20.1 \stackrel{\times}{\div} \exp(1.96/\sqrt{D}) = (12.5, 32.4)$$

per 1000 person-years.

Ratio of two rates

If we have observations two rates λ_1 and λ_0, based on (D_1, Y_1) and (D_0, Y_0), the variance of the difference of the log-rates, the $\log(\text{RR})$, is:

$$\begin{aligned} \text{var}(\log(\text{RR})) &= \text{var}(\log(\lambda_1/\lambda_0)) \\ &= \text{var}(\log(\lambda_1)) + \text{var}(\log(\lambda_0)) \\ &= 1/D_1 + 1/D_0 \end{aligned}$$

As before a 95% c.i. for the RR is then:

$$\text{RR} \stackrel{\times}{\div} \underbrace{\exp\left(1.96\sqrt{\frac{1}{D_1} + \frac{1}{D_0}}\right)}_{\text{error factor}}$$

Example

Suppose we in group 0 have 17 deaths during 843.6 years of follow-up in one group, and in group 1 have 28 deaths during 632.3 years.

The rate-ratio is computed as:

$$\begin{aligned} \text{RR} &= \hat{\lambda}_1/\hat{\lambda}_0 = (D_1/Y_1)/(D_0/Y_0) \\ &= (28/632.3)/(17/843.7) = 0.0443/0.0201 = 2.198 \end{aligned}$$

The 95% confidence interval is computed as:

$$\begin{aligned} \hat{\text{RR}} \stackrel{\times}{\div} \text{erf} &= 2.198 \stackrel{\times}{\div} \exp\left(1.96\sqrt{1/17 + 1/28}\right) \\ &= 2.198 \stackrel{\times}{\div} 1.837 = (1.20, 4.02) \end{aligned}$$

Example using R

Poisson likelihood, for one rate,
based on 17 events in 843.7 PY:

```
library( Epi )
D <- 17 ; Y <- 843.7
m1 <- glm( D ~ 1, offset=log(Y/1000), family=poisson)
ci.exp( m1 )
```

```
            exp(Est.)     2.5%    97.5%
(Intercept)  20.14934 12.52605 32.41213
```

Poisson likelihood, two rates, or one rate and RR:

```
D <- c(17,28) ; Y <- c(843.7,632.3) ; gg <- factor(0:1)
m2 <- glm( D ~ gg, offset=log(Y/1000), family=poisson)
ci.exp( m2 )
```

```
            exp(Est.)      2.5%     97.5%
(Intercept) 20.149342 12.526051 32.412130
gg1          2.197728  1.202971  4.015068
```


Example using R

Poisson likelihood, two rates, or one rate and RR:

```
D <- c(17,28) ; Y <- c(843.7,632.3) ; gg <- factor(0:1)
m2 <- glm( D ~ gg, offset=log(Y/1000), family=poisson)
ci.exp( m2 )
```

```
            exp(Est.)      2.5%     97.5%
(Intercept) 20.149342 12.526051 32.412130
gg1          2.197728  1.202971  4.015068
```

```
m3 <- glm( D ~ gg - 1, offset=log(Y/1000), family=poisson)
ci.exp( m3 )
```

```
    exp(Est.)     2.5%    97.5%
gg0  20.14934 12.52605 32.41213
gg1  44.28278 30.57545 64.13525
```


Representation of follow-up data

Bendix Carstensen
Senior Statistician, Steno Diabetes Center

Practice in analysis of multistate models using `Epi::Lexis`
University of Aberdeen,
18 AUgust 2017

`http://BendixCarstensen/AdvCoh/courses/Frias-2016` time-split

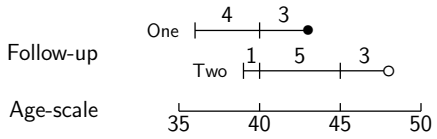
Follow-up and rates

- Follow-up studies:
  - D — events, deaths
  - Y — person-years
  - $\lambda = D/Y$ rates
- Rates differ between persons.
- Rates differ within persons:
  - By age
  - By calendar time
  - By disease duration
  - ...
- Multiple timescales.
- Multiple states (little boxes — later)

Stratification by age

If follow-up is rather short, age at entry is OK for age-stratification.

If follow-up is long, use stratification by categories of **current age**, both for:
No. of events, D, and Risk time, Y.



Representation of follow-up data

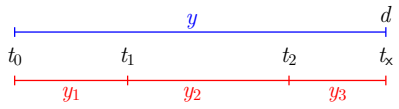
A cohort or follow-up study records:
Events and **Risk time**.

The outcome is thus **bivariate**: (d, y)

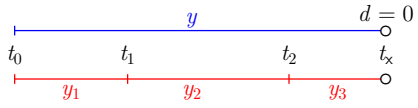
Follow-up **data** for each individual must therefore have (at least) three variables:

Date of entry	`entry`	date variable
Date of exit	`exit`	date variable
Status at exit	`fail`	indicator (0/1)

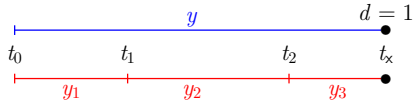
Specific for each **type** of outcome.



Probability	log-Likelihood
$\mathrm{P}(d \text{ at } t_x \mid \text{entry } t_0)$	$d\log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_0 \to t_1 \mid \text{entry } t_0)$	$= 0\log(\lambda) - \lambda y_1$
$\times \mathrm{P}(\text{surv } t_1 \to t_2 \mid \text{entry } t_1)$	$+ 0\log(\lambda) - \lambda y_2$
$\times \mathrm{P}(d \text{ at } t_x \mid \text{entry } t_2)$	$+ d\log(\lambda) - \lambda y_3$



Probability	log-Likelihood
$\mathrm{P}(\text{surv } t_0 \to t_x \mid \text{entry } t_0)$	$0\log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_0 \to t_1 \mid \text{entry } t_0)$	$= 0\log(\lambda) - \lambda y_1$
$\times \mathrm{P}(\text{surv } t_1 \to t_2 \mid \text{entry } t_1)$	$+ 0\log(\lambda) - \lambda y_2$
$\times \mathrm{P}(\text{surv } t_2 \to t_x \mid \text{entry } t_2)$	$+ 0\log(\lambda) - \lambda y_3$



Probability	log-Likelihood
$\mathrm{P}(\text{event at } t_x \mid \text{entry } t_0)$	$1\log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_0 \to t_1 \mid \text{entry } t_0)$	$= 0\log(\lambda) - \lambda y_1$
$\times \mathrm{P}(\text{surv } t_1 \to t_2 \mid \text{entry } t_1)$	$+ 0\log(\lambda) - \lambda y_2$
$\times \mathrm{P}(\text{event at } t_x \mid \text{entry } t_2)$	$+ 1\log(\lambda) - \lambda y_3$

Dividing time into bands:

If we want to put D and Y into intervals on the timescale we must know:

Origin: The date where the time scale is 0:

- Age — 0 at date of birth
- Disease duration — 0 at date of diagnosis
- Occupation exposure — 0 at date of hire

Intervals: How should it be subdivided:

- 1-year classes? 5-year classes?
- Equal length?

Aim: Separate rate in each interval

Example: cohort with 3 persons:

```
Id      Bdate      Entry       Exit St
 1 14/07/1952 04/08/1965 27/06/1997  1
 2 01/04/1954 08/09/1972 23/05/1995  0
 3 10/06/1987 23/12/1991 24/07/1998  1
```

- Age bands: 10-years intervals of current age.
- Split Y for every subject accordingly
- Treat each segment as a separate unit of observation.
- Keep track of exit status in each interval.

Splitting the follow up

	subj. 1	subj. 2	subj. 3
Age at **E**ntry:	13.06	18.44	4.54
Age at e**X**it:	44.95	41.14	11.12
Status at exit:	Dead	Alive	Dead
Y	31.89	22.70	6.58
D	1	0	1

	subj. 1		subj. 2		subj. 3		$\sum$	
Age	Y	D	Y	D	Y	D	Y	D
0–	0.00	0	0.00	0	5.46	0	5.46	0
10–	6.94	0	1.56	0	1.12	1	8.62	1
20–	10.00	0	10.00	0	0.00	0	20.00	0
30–	10.00	0	10.00	0	0.00	0	20.00	0
40–	4.95	1	1.14	0	0.00	0	6.09	1
$\sum$	31.89	1	22.70	0	6.58	1	60.17	2

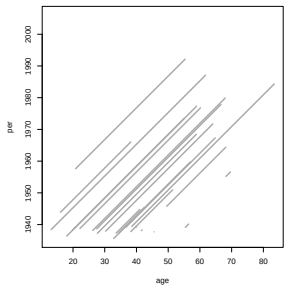
Splitting the follow-up

```
id      Bdate      Entry       Exit  St     risk  int
 1 14/07/1952 03/08/1965 14/07/1972   0   6.9432   10
 1 14/07/1952 14/07/1972 14/07/1982   0  10.0000   20
 1 14/07/1952 14/07/1982 14/07/1992   0  10.0000   30
 1 14/07/1952 14/07/1992 27/06/1997   1   4.9528   40
 2 01/04/1954 08/09/1972 01/04/1974   0   1.5606   10
 2 01/04/1954 01/04/1974 31/03/1984   0  10.0000   20
 2 01/04/1954 31/03/1984 01/04/1994   0  10.0000   30
 2 01/04/1954 01/04/1994 23/05/1995   0   1.1417   40
 3 10/06/1987 23/12/1991 09/06/1997   0   5.4634    0
 3 10/06/1987 09/06/1997 24/07/1998   1   1.1211   10
```

Keeping track of calendar time too?

Timescales

- A timescale is a variable that varies **deterministically** *within* each person during follow-up:
  - Age
  - Calendar time
  - Time since treatment
  - Time since relapse
- All timescales advance at the same pace (1 year per year . . .)
- Note: Cumulative exposure is **not** a timescale.



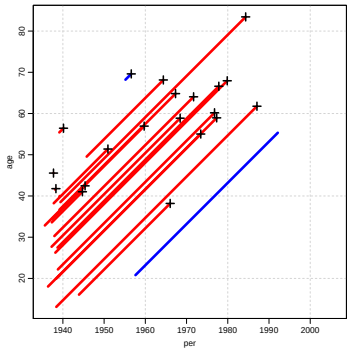

```
> plot( thL, lwd=3 )
```


Follow-up on several timescales

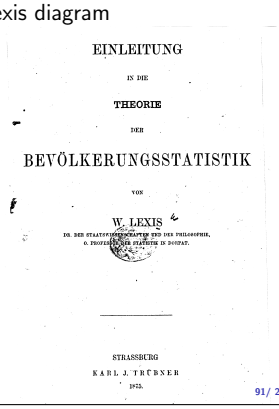
- The risk-time is the same on all timescales
- Only need the entry point on each time scale:
  - Age at entry.
  - Date of entry.
  - Time since treatment at entry.
    — if time of treatment is the entry, this is 0 for all.
- Response variable in analysis of rates:

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

- Covariates in analysis of rates:
  - timescales
  - other (fixed) measurements



Lexis diagram


EINLEITUNG

IN DIE

THEORIE

DER

BEVÖLKERUNGSSTATISTIK

VON

W. LEXIS

STRASSBURG

KARL J. TRÜBNER

1875.

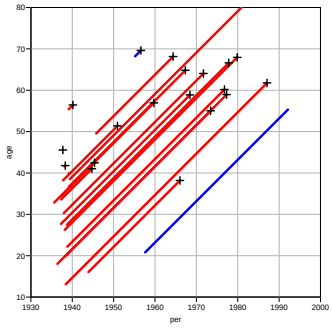
Follow-up data in `Epi` — `Lexis` objects

A follow-up study:

```
> round( th, 2 )
    id sex birthdat contrast injecdat volume exitdat exitstat
1    1   2  1916.61        1  1938.79     22 1976.79        1
2  640   2  1896.23        1  1945.77     20 1964.37        1
3 3425   1  1886.97        2  1955.18      0 1956.59        1
4 4017   2  1936.81        2  1957.61      0 1992.14        2
...
```

Timescales of interest:

- Age
- Calendar time
- Time since injection




```
> plot( thL, 2:1, lwd=5, col=c("red","blue")[thL$contrast],
+       grid=TRUE, lty.grid=1, col.grid=gray(0.7),
+       xlim=1930+c(0,70), xaxs="i", ylim=  10+c(0,70), yaxs="i", las=1 )
> points( thL, 2:1, pch=c(NA,3)[thL$lex.Xst+1],lwd=3, cex=1.5 )
```


Definition of `Lexis` object

```
> thL <- Lexis( entry = list( age = injecdat-birthdat,
+                             per = injecdat,
+                             tfi = 0 ),
+               exit = list( per = exitdat ),
+         exit.status = as.numeric(exitstat==1),
+               data = th )
```

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

`exitdat - injecdat`

Splitting follow-up time

```
> spl1 <- splitLexis( thL, breaks=seq(0,100,20),
>                          time.scale="age" )
> round(spl1,1)
   age    per  tfi lex.dur lex.Cst lex.Xst   id sex birthdat contrast injecdat vol
1 22.2 1938.8  0.0    17.8       0       0    1   2   1916.6        1   1938.8
2 40.0 1956.6 17.8    20.0       0       0    1   2   1916.6        1   1938.8
3 60.0 1976.6 37.8     0.2       0       1    1   2   1916.6        1   1938.8
4 49.5 1945.8  0.0    10.5       0       0  640   2   1896.2        1   1945.8
5 60.0 1956.2 10.5     8.1       0       1  640   2   1896.2        1   1945.8
6 68.2 1955.2  0.0     1.4       0       1 3425   1   1887.0        2   1955.2
7 20.8 1957.6  0.0    19.2       0       0 4017   2   1936.8        2   1957.6
8 40.0 1976.8 19.2    15.3       0       0 4017   2   1936.8        2   1957.6
...
```

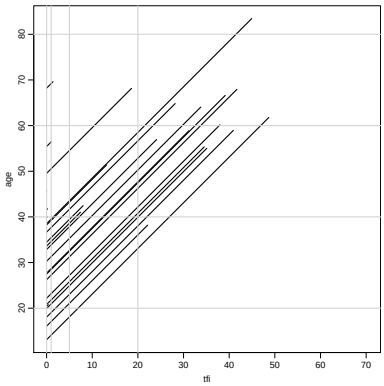

The looks of a `Lexis` object

```
> thL[,1:9]
    age      per tfi lex.dur lex.Cst lex.Xst lex.id
1 22.18 1938.79   0   37.99       0       1      1
2 49.54 1945.77   0   18.59       0       1      2
3 68.20 1955.18   0    1.40       0       1      3
4 20.80 1957.61   0   34.52       0       0      4
...

> summary( thL )
Transitions:
     To
From 0  1 Records:  Events:  Risk time:  Persons:
   0 3 20        23       20      512.59        23
```


Split on another timescale

```
> spl2 <- splitLexis( spl1, time.scale="tfi",
                            breaks=c(0,1,5,20,100) )
> round( spl2, 1 )
   lex.id  age    per  tfi lex.dur lex.Cst lex.Xst   id sex birthdat contrast inje
1       1 22.2 1938.8  0.0     1.0       0       0    1   2   1916.6        1   19
2       1 23.2 1939.8  1.0     4.0       0       0    1   2   1916.6        1   19
3       1 27.2 1943.8  5.0    12.8       0       0    1   2   1916.6        1   19
4       1 40.0 1956.6 17.8     2.2       0       0    1   2   1916.6        1   19
5       1 42.2 1958.8 20.0    17.8       0       0    1   2   1916.6        1   19
6       1 60.0 1976.6 37.8     0.2       0       1    1   2   1916.6        1   19
7       2 49.5 1945.8  0.0     1.0       0       0  640   2   1896.2        1   19
8       2 50.5 1946.8  1.0     4.0       0       0  640   2   1896.2        1   19
9       2 54.5 1950.8  5.0     5.5       0       0  640   2   1896.2        1   19
10      2 60.0 1956.2 10.5     8.1       0       1  640   2   1896.2        1   19
11      3 68.2 1955.2  0.0     1.0       0       0 3425   1   1887.0        2   19
12      3 69.2 1956.2  1.0     0.4       0       1 3425   1   1887.0        2   19
13      4 20.8 1957.6  0.0     1.0       0       0 4017   2   1936.8        2   19
14      4 21.8 1958.6  1.0     4.0       0       0 4017   2   1936.8        2   19
15      4 25.8 1962.6  5.0    14.2       0       0 4017   2   1936.8        2   19
16      4 40.0 1976.8 19.2     0.8       0       0 4017   2   1936.8        2   19
17      4 40.8 1977.6 20.0    14.5       0       0 4017   2   1936.8        2   19
```



age	tfi	lex.dur	lex.Cst	lex.Xst
22.2	0.0	1.0	0	0
23.2	1.0	4.0	0	0
27.2	5.0	12.8	0	0
40.0	17.8	2.2	0	0
42.2	20.0	17.8	0	0
60.0	37.8	0.2	0	1

Survival analysis

- Response variable: Time to event, T
- Censoring time, Z
- We observe $(\min(T, Z), \delta = 1\{T < Z\})$.
- This gives time a special status, and mixes the response variable (risk)time with the covariate time(scale).
- Originates from clinical trials where everyone enters at time 0, and therefore $Y = T - 0 = T$

Likelihood for a piecewise constant rate

- This setup is for a situation where it is assumed that rates are constant in each of the intervals.
- Each observation in the dataset contributes a term to a "Poisson" likelihood.
- Models can include fixed covariates, as well as the timescales (the left end-points of the intervals) as continuous variables.
- Rates are assumed to vary by timescales:
  - continuously
  - non-linearly
- Rates can vary along several timescales simultaneously.

The life table method

The simplest analysis is by the "life-table method":

interval i	alive n_i	dead d_i	cens. l_i	p_i
1	77	5	2	$5/(77-2/2)=0.066$
2	70	7	4	$7/(70-4/2)=0.103$
3	59	8	1	$8/(59-1/2)=0.137$

$$\begin{aligned} p_i &= \mathrm{P}\{\text{death in interval } i\} = 1 - d_i/(n_i - l_i/2) \\ S(t) &= (1-p_1) \times \cdots \times (1-p_t) \end{aligned}$$

Where is (d_{pi}, y_{pi}) in the split data?

Likelihood is $d_{pi}\log(\lambda_{pi}) - \lambda_{pi} y_{pi}$

```
> round( spl2, 1 )
   lex.id  age    per  tfi lex.dur lex.Cst lex.Xst   id sex birthdat contrast
1       1 22.2 1938.8  0.0     1.0       0       0    1   2   1916.6        1
2       1 23.2 1939.8  1.0     4.0       0       0    1   2   1916.6        1
3       1 27.2 1943.8  5.0    12.8       0       0    1   2   1916.6        1
4       1 40.0 1956.6 17.8     2.2       0       0    1   2   1916.6        1
5       1 42.2 1958.8 20.0    17.8       0       0    1   2   1916.6        1
6       1 60.0 1976.6 37.8     0.2       0       1    1   2   1916.6        1
7       2 49.5 1945.8  0.0     1.0       0       0  640   2   1896.2        1
8       2 50.5 1946.8  1.0     4.0       0       0  640   2   1896.2        1
9       2 54.5 1950.8  5.0     5.5       0       0  640   2   1896.2        1
10      2 60.0 1956.2 10.5     8.1       0       1  640   2   1896.2        1
...
```

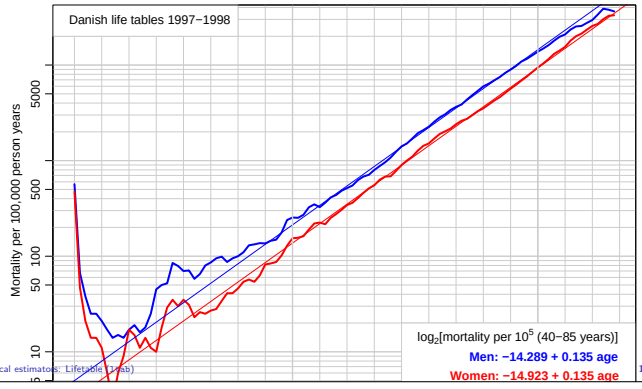
— and what are **covariates** for the rates?

Population life table, DK 1997–98

	Men			Women		
a	$S(a)$	$\lambda(a)$	$\mathrm{E}[\ell_{\mathrm{res}}(a)]$	$S(a)$	$\lambda(a)$	$\mathrm{E}[\ell_{\mathrm{res}}(a)]$
0	1.00000	567	73.68	1.00000	474	78.65
1	0.99433	67	73.10	0.99526	47	78.02
2	0.99366	38	72.15	0.99479	21	77.06
3	0.99329	25	71.18	0.99458	14	76.08
4	0.99304	25	70.19	0.99444	14	75.09
5	0.99279	21	69.21	0.99430	11	74.10
6	0.99258	17	68.23	0.99419	6	73.11
7	0.99242	14	67.24	0.99413	3	72.11
8	0.99227	15	66.25	0.99410	6	71.11
9	0.99213	14	65.26	0.99404	9	70.12
10	0.99199	17	64.26	0.99395	17	69.12
11	0.99181	19	63.28	0.99378	15	68.14
12	0.99162	16	62.29	0.99363	11	67.15
13	0.99147	18	61.30	0.99352	14	66.15
14	0.99129	25	60.31	0.99338	11	65.16
15	0.99104	45	59.32	0.99327	10	64.17
16	0.99059	50	58.35	0.99317	18	63.18
17	0.99009	52	57.38	0.99299	29	62.19
18	0.98957	85	56.41	0.99270	35	61.21
19	0.98873	79	55.46	0.99235	30	60.23
20	0.98795	70	54.50	0.99205	35	59.24
21	0.98726	71	53.54	0.99170	31	58.27

Analysis of results

- d_{pi} — events in the variable: `lex.Xst`:
  In the model as response: `lex.Xst==1`
- y_{pi} — risk time: `lex.dur` (duration):
  In the model as offset $\log(y)$, `log(lex.dur)`.
- Covariates are:
  - timescales (age, period, time in study)
  - other variables for this person (constant or *assumed* constant in each interval).
- Model rates using the covariates in `glm`:
  — no difference between time-scales and other covariates.



Classical estimators: Lifetable

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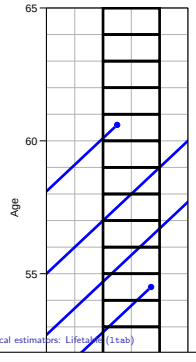
Practice in analysis of multistate models using `Epi::Lexis`
University of Aberdeen,
18 AUgust 2017

`http://BendixCarstensen/AdvCoh/courses/Frias-2016` `ltab`

Observations for the lifetable



Life table is based on person-years and deaths accumulated in a short period.

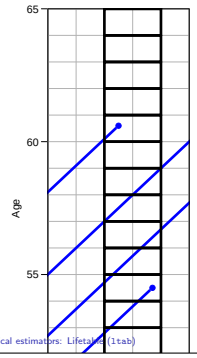
Age-specific rates — cross-sectional!

Survival function:

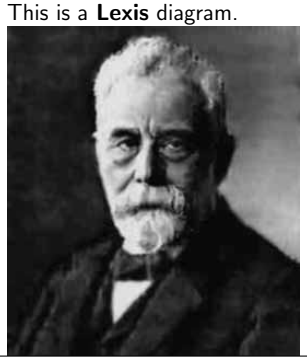
$$S(t) = \mathrm{e}^{-\int_0^t \lambda(a)\,\mathrm{d}a} = \mathrm{e}^{-\sum_0^t \lambda(a)}$$

— assumes stability of rates to be interpretable for actual persons.

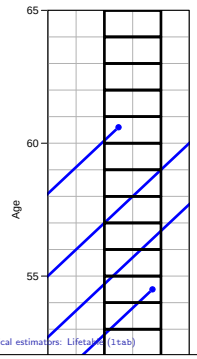
Observations for the lifetable



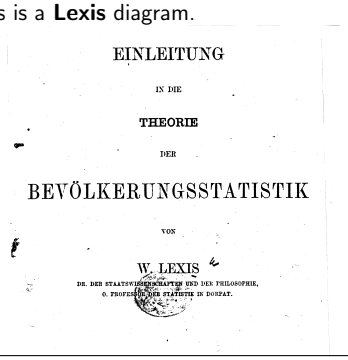
This is a **Lexis** diagram.



Observations for the lifetable



This is a **Lexis** diagram.


EINLEITUNG

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W. LEXIS

Life table approach

individual.

- The **population** experience:
  - D: Deaths (events).
  - Y: Person-years (risk time).
- The classical lifetable analysis compiles these for prespecified intervals of age, and computes age-specific mortality **rates**.
- Data are collected crossectionally, but interpreted longitudinally.
- The **rates** are the basic building bocks — used for construction of:
  - RRs
  - cumulative measures (survival and risk)

Summary

- Follow-up studies observe time to event
- — in the form of **empirical rates**, (d, y) for small interval
- each interval (empirical rate) has covariates attached
- each interval contribute $d\log(\lambda) - \lambda y$
- — like a Poisson observation d with mean λy
- identical covariates: pool obervations to $D = \sum D$, $Y = \sum y$
- — like a Poisson obervation D with mean λY
- the result is an **estimate** of the rate λ
- from a **model** where rates are constant within intervals — but varies between intervals.

Classical estimators: Kaplan-Meier

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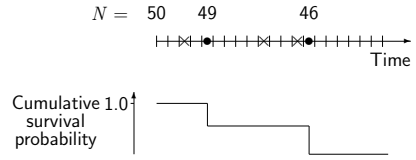
`http://BendixCarstensen/AdvCoh/courses/Frias-2016` km-na

The Kaplan-Meier Method

- The most common method of estimating the survival function.
- A non-parametric method.
- Divides time into small intervals where the intervals are defined by the unique times of failure (death).
- Based on conditional probabilities as we are interested in the probability a subject surviving the next time interval given that they have survived so far.

Kaplan–Meier method illustrated

($\bullet$ = failure and $\times$ = censored):



- Steps caused by multiplying by $(1 - 1/49)$ and $(1 - 1/46)$ respectively
- Late entry can also be dealt with

Using R: `Surv()`

```
library( survival )
data( lung )
head( lung, 3 )
```

```
  inst time status age sex ph.ecog ph.karno pat.karno meal.cal wt.loss
1    3  306      2  74   1       1        90       100      1175      NA
2    3  455      2  68   1       0        90        90      1225      15
3    3 1010      1  56   1       0        90        90        NA      15
```

```
with( lung, Surv( time, status==2 ) )[1:10]
```

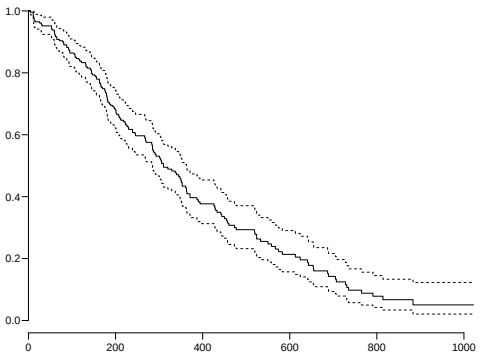
```
 [1]  306   455  1010+  210   883  1022+  310   361   218   166
```

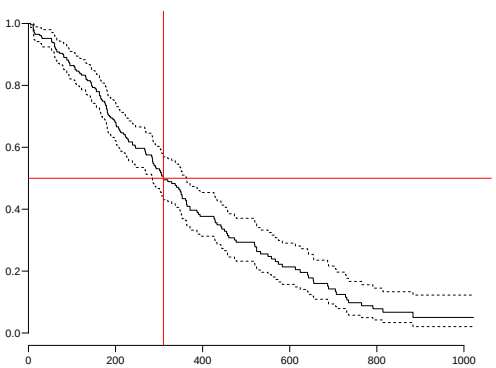
```
( s.km <- survfit( Surv( time, status==2 ) ~ 1 , data=lung ) )
```

```
Call: survfit(formula = Surv(time, status == 2) ~ 1, data = lung)

      n  events  median 0.95LCL 0.95UCL
    228     165     310     285     363
```

```
plot( s.km )
abline( v=310, h=0.5, col="red" )
```



Who needs the Cox-model anyway?

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University of Aberdeen,
18 AUgust 2017

`http://BendixCarstensen/AdvCoh/courses/Frias-2016` KMCox

A look at the Cox model

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

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

The covariate t has a special status:

- Computationally, because all individuals contribute to (some of) the range of t.
- . . . the scale along which time is split (the risk sets)
- Conceptually t is just a covariate that varies within individual.
- Cox's approach profiles $\lambda_0(t)$ out from the model

The Cox-likelihood as profile likelihood

- One parameter per death time to describe the effect of time (i.e. the chosen timescale).

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

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

The Cox-likelihood: mechanics of computing

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

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

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

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

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

Note: There is one contribution from each person at risk to this part of the log-likelihood:

$$\begin{aligned}
\ell_t(\alpha_t,\beta) &= \sum_{i\in\mathcal{R}_t} d_i \log(\lambda_i(t)) - \lambda_i(t) y_i \\
&= \sum_{i\in\mathcal{R}_t} \left\{ d_i(\alpha_t+\eta_i) - e^{\alpha_t+\eta_i} \right\} \\
&= \alpha_t + \eta_{\text{death}} - e^{\alpha_t} \sum_{i\in\mathcal{R}_t} e^{\eta_i}
\end{aligned}$$

where η_{death} is the linear predictor for the person that died.

The derivative w.r.t. α_t is:

$$D_{\alpha_t}\ell_t(\alpha_t,\beta) = 1 - e^{\alpha_t}\sum_{i\in\mathcal{R}_t} e^{\eta_i} = 0 \quad\Leftrightarrow\quad e^{\alpha_t} = \frac{1}{\sum_{i\in\mathcal{R}_t} e^{\eta_i}}$$

If this estimate is fed back into the log-likelihood for α_t, we get the **profile likelihood** (with α_t "profiled out"):

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

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

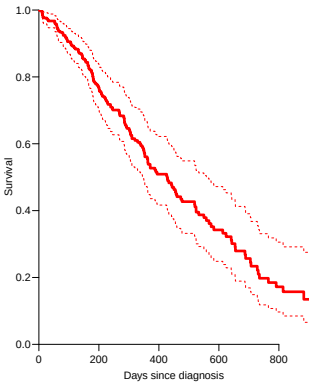
Splitting the dataset a priori

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

Example: Mayo Clinic lung cancer

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

Mayo Clinic lung cancer 60 year old woman



Example: Mayo Clinic lung cancer I

```
> library( survival )
> library( Epi )
> Lung <- Lexis( exit = list( tfe=time ),
+                exit.status = factor(status,labels=c("Alive","Dead")),
+                data = lung )

NOTE: entry.status has been set to "Alive" for all.
NOTE: entry is assumed to be 0 on the tfe timescale.
```


Example: Mayo Clinic lung cancer II

```
> mL.cox <- coxph( Surv( tfe, tfe+lex.dur, lex.Xst=="Dead" ) ~
+                  age + factor( sex ),
+                  method="breslow", eps=10^-8, iter.max=25, data=Lung )
> Lung.s <- splitLexis( Lung,
+                       breaks=c(0,sort(unique(Lung$time))),
+                       time.scale="tfe" )
> Lung.S <- splitLexis( Lung,
+                       breaks=c(0,sort(unique(Lung$time[Lung$lex.Xst=="Dead"]))),
+                       time.scale="tfe" )
> summary( Lung.s )

Transitions:
     To
From    Alive Dead  Records:  Events: Risk time:  Persons:
  Alive 19857  165     20022      165      69593       228

> summary( Lung.S )
```


Example: Mayo Clinic lung cancer III

```
Transitions:
     To
From    Alive Dead  Records:  Events: Risk time:  Persons:
  Alive 15916  165     16081      165      69593       228

> subset( Lung.s, lex.id==96 )[,1:11]

     lex.id tfe lex.dur lex.Cst lex.Xst inst time status age sex ph.ecog
9235     96   0       5   Alive   Alive   12   30      2  72   1        2
9236     96   5       6   Alive   Alive   12   30      2  72   1        2
9237     96  11       1   Alive   Alive   12   30      2  72   1        2
9238     96  12       1   Alive   Alive   12   30      2  72   1        2
9239     96  13       2   Alive   Alive   12   30      2  72   1        2
9240     96  15      11   Alive   Alive   12   30      2  72   1        2
9241     96  26       4   Alive    Dead   12   30      2  72   1        2

> nlevels( factor( Lung.s$tfe ) )

[1] 186
```


Example: Mayo Clinic lung cancer IV

```
> system.time(
+ mLs.pois.fc <- glm( lex.Xst=="Dead" ~ - 1 + factor( tfe ) +
+                                 age + factor( sex ),
+                                 offset = log(lex.dur),
+                     family=poisson, data=Lung.s, eps=10^-8, maxit=25 )
+             )

   user  system elapsed
 10.540   0.016  10.555

> length( coef(mLs.pois.fc) )

[1] 188

> system.time(
+ mLS.pois.fc <- glm( lex.Xst=="Dead" ~ - 1 + factor( tfe ) +
+                                 age + factor( sex ),
+                                 offset = log(lex.dur),
+                     family=poisson, data=Lung.S, eps=10^-8, maxit=25 )
+             )
```


Example: Mayo Clinic lung cancer V

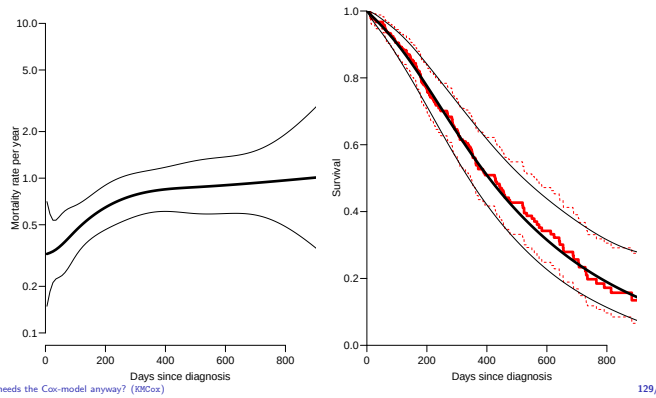
```
    user  system elapsed
   3.175   0.003   3.178

> length( coef(mLS.pois.fc) )

[1] 142

> t.kn <- c(0,25,100,500,1000)
> dim( Ns(Lung.s$tfe,knots=t.kn) )

[1] 20022     4

> system.time(
+ mLs.pois.sp <- glm( lex.Xst=="Dead" ~ Ns( tfe, knots=t.kn ) +
+                                 age + factor( sex ),
+                     offset = log(lex.dur),
+                     family=poisson, data=Lung.s, eps=10^-8, maxit=25 )
+             )
```

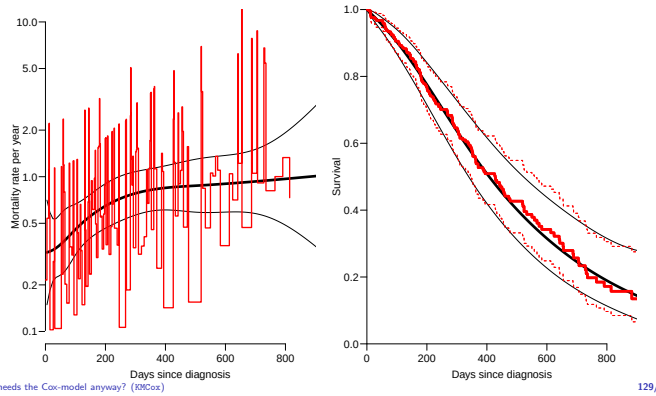

Example: Mayo Clinic lung cancer VI

```
    user  system elapsed
   0.227   0.000   0.227

> ests <-
+ rbind( ci.exp(mL.cox),
+        ci.exp(mLs.pois.fc,subset=c("age","sex")),
+        ci.exp(mLS.pois.fc,subset=c("age","sex")),
+        ci.exp(mLs.pois.sp,subset=c("age","sex")) )
> cmp <- cbind( ests[c(1,3,5,7)  ,],
+               ests[c(1,3,5,7)+1,] )
> rownames( cmp ) <- c("Cox","Poisson-factor","Poisson-factor (D)","Poisson-spline
> colnames( cmp )[c(1,4)] <- c("age","sex")



> round( cmp, 7 )
```


Example: Mayo Clinic lung cancer VII

	age	2.5%	97.5%	sex	2.5%	97.5%
Cox	1.017158	0.9989388	1.035710	0.5989574	0.4313720	0.8316487
Poisson-factor	1.017158	0.9989388	1.035710	0.5989574	0.4313720	0.8316487
Poisson-factor (D)	1.017332	0.9991211	1.035874	0.5984794	0.4310150	0.8310094
Poisson-spline	1.016189	0.9980329	1.034676	0.5998287	0.4319932	0.8328707





Deriving the survival function

```
> mLs.pois.sp <- glm( lex.Xst=="Dead" ~ Ns( tfe, knots=t.kn ) +
+                                 age + factor( sex ),
+                     offset = log(lex.dur),
+                     family=poisson, data=Lung.s, eps=10^-8, maxit=25 )



> CM <- cbind( 1, Ns( seq(10,1000,10)-5, knots=t.kn ), 60, 1 )
> lambda <- ci.exp( mLs.pois.sp, ctr.mat=CM )
> Lambda <- ci.cum( mLs.pois.sp, ctr.mat=CM, intl=10 )[,-4]
> survP  <- exp(-rbind(0,Lambda))
```

Code and output for the entire example avaiable in
`http://bendixcarstensen.com/AdvCoh/WNtCMa/`

What the Cox-model really is

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

- dividing time very finely and
- modeling one covariate, the time-scale, with one parameter per distinct value.
- the **model** for the time scale is really with exchangeable time-intervals.
- $\Rightarrow$ difficult to access the baseline hazard (which looks terrible)
- $\Rightarrow$ uninitiated tempted to show survival curves where irrelevant

Models of this world

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

Multiple time scales and continuous rates

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`http://BendixCarstensen/AdvCoh/courses/Frias-2016` crv-mod

Testis cancer

Testis cancer in Denmark:

```
> options( show.signif.stars=FALSE )
> library( Epi )
> data( testisDK )
> str( testisDK )

'data.frame': 4860 obs. of  4 variables:
 $ A: num  0 1 2 3 4 5 6 7 8 9 ...
 $ P: num  1943 1943 1943 1943 1943 ...
 $ D: num  1 1 0 1 0 0 0 0 0 0 ...
 $ Y: num  39650 36943 34588 33267 32614 ...

> head( testisDK )

  A    P D        Y
1 0 1943 1 39649.50
2 1 1943 1 36942.83
3 2 1943 0 34588.33
4 3 1943 1 33267.00
5 4 1943 0 32614.00
6 5 1943 0 32020.33
```


Cases, PY and rates

```
> stat.table( list(A=floor(A/10)*10,
+                  P=floor(P/10)*10),
+             list( D=sum(D),
+                   Y=sum(Y/1000),
+                rate=ratio(D,Y,10^5) ),
+             margins=TRUE, data=testisDK )
```

	P					
A	1940	1950	1960	1970	1980	1990	Total
0	10.00	7.00	16.00	18.00	9.00	10.00	70.00
	2604.66	4037.31	3884.97	3820.88	3070.87	2165.54	19584.22
	0.38	0.17	0.41	0.47	0.29	0.46	0.36
10	13.00	27.00	37.00	72.00	97.00	75.00	321.00
	2135.73	3505.19	4004.13	3906.08	3847.40	2260.97	19659.48
	0.61	0.77	0.92	1.84	2.52	3.32	1.63
20	124.00	221.00	280.00	535.00	724.00	557.00	2441.00
	2225.55	2923.22	3401.65	4028.57	3941.18	2824.58	19344.74
	5.57	7.56	8.23	13.28	18.37	19.72	12.62

Linear effects in `glm`

How do rates depend on age?

```
> ml <- glm( D ~ A, offset=log(Y), family=poisson, data=testisDK )
> round( ci.lin( ml ), 4 )

             Estimate StdErr          z P    2.5%   97.5%
(Intercept)  -9.7755 0.0207 -472.3164 0 -9.8160 -9.7349
A             0.0055 0.0005   11.3926 0  0.0045  0.0064

> round( ci.exp( ml ), 4 )

             exp(Est.)   2.5%  97.5%
(Intercept)     0.0001 0.0001 0.0001
A               1.0055 1.0046 1.0064
```

Linear increase of log-rates by age

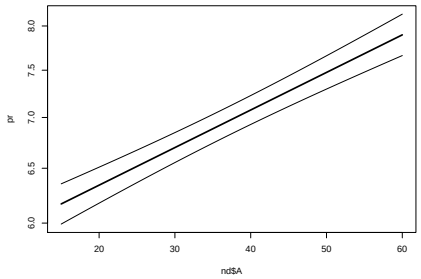
Linear effects in `glm`

```
> nd <- data.frame( A=15:60, Y=10^5 )
> pr <- ci.pred( ml, newdata=nd )
> head( pr )

  Estimate     2.5%    97.5%
1 6.170105 5.991630 6.353896
2 6.204034 6.028525 6.384652
3 6.238149 6.065547 6.415662
4 6.272452 6.102689 6.446937
5 6.306943 6.139944 6.478485
6 6.341624 6.177301 6.510319

> matplot( nd$A, pr,
+          type="l", lty=1, lwd=c(3,1,1), col="black", log="y" )
```


Linear effects in `glm`

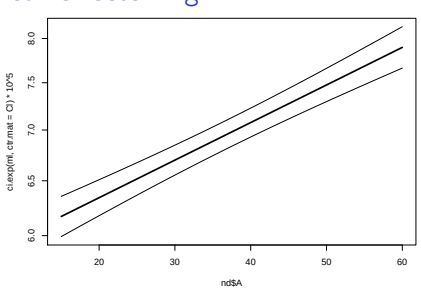
```
> round( ci.lin( ml ), 4 )

             Estimate StdErr          z P    2.5%   97.5%
(Intercept)  -9.7755 0.0207 -472.3164 0 -9.8160 -9.7349
A             0.0055 0.0005   11.3926 0  0.0045  0.0064

> Cl <- cbind( 1, nd$A )
> head( Cl )

     [,1] [,2]
[1,]    1   15
[2,]    1   16
[3,]    1   17
[4,]    1   18
[5,]    1   19
[6,]    1   20

> matplot( nd$A, ci.exp( ml, ctr.mat=Cl ),
+          type="l", lty=1, lwd=c(3,1,1), col="black", log="y" )
```


Linear effects in `glm`




```
> matplot( nd$A, pr,
+          type="l", lty=1, lwd=c(3,1,1), col="black", log="y" )
```


Linear effects in `glm`




```
> matplot( nd$A, ci.exp( ml, ctr.mat=Cl )*10^5,
+          type="l", lty=1, lwd=c(3,1,1), col="black", log="y" )
```

Quadratic effects in glm

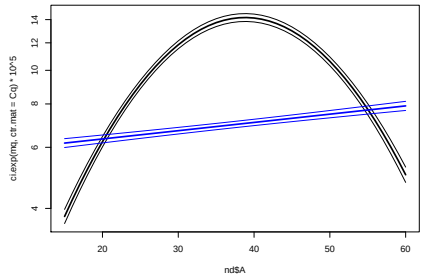
How do rates depend on age?

```
> mq <- glm( D ~ A + I(A^2),
+           offset=log(Y), family=poisson, data=testisDK )
> round( ci.lin( mq ), 4 )

            Estimate StdErr         z P     2.5%    97.5%
(Intercept) -12.3656 0.0596 -207.3611 0 -12.4825 -12.2487
A             0.1806 0.0033   54.8290 0   0.1741   0.1871
I(A^2)       -0.0023 0.0000  -53.7006 0  -0.0024  -0.0022

> round( ci.exp( mq ), 4 )

            exp(Est.)   2.5%  97.5%
(Intercept)    0.0000 0.0000 0.0000
A              1.1979 1.1902 1.2057
I(A^2)         0.9977 0.9976 0.9978
```


Quadratic effect in glm

```
> round( ci.lin( mq ), 4 )

            Estimate StdErr         z P     2.5%    97.5%
(Intercept) -12.3656 0.0596 -207.3611 0 -12.4825 -12.2487
A             0.1806 0.0033   54.8290 0   0.1741   0.1871
I(A^2)       -0.0023 0.0000  -53.7006 0  -0.0024  -0.0022

> Cq <- cbind( 1, 15:60, (15:60)^2 )
> head( Cq, 4 )

     [,1] [,2] [,3]
[1,]    1   15  225
[2,]    1   16  256
[3,]    1   17  289
[4,]    1   18  324

> matplot( nd$A, ci.exp( mq, ctr.mat=Cq )*10^5,
+          type="l", lty=1, lwd=c(3,1,1), col="black", log="y" )
```


Quadratic effect in glm

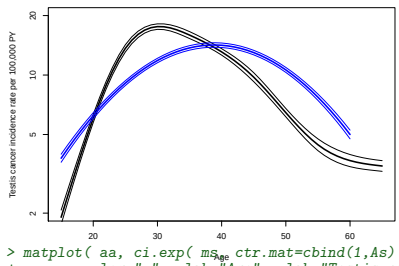



```
> matplot( nd$A, ci.exp( mq, ctr.mat=Cq )*10^5,
+          type="l", lty=1, lwd=c(3,1,1), col="black", log="y" )
> matlines( nd$A, ci.exp( ml, ctr.mat=Cl )*10^5,
+           type="l", lty=1, lwd=c(3,1,1), col="blue" )
```


Spline effects in glm

```
> library( splines )
> ms <- glm( D ~ Ns(A,knots=seq(15,65,10)),
+            offset=log(Y), family=poisson, data=testisDK )
> round( ci.exp( ms ), 3 )

                                exp(Est.)   2.5%  97.5%
(Intercept)                         0.000  0.000  0.000
Ns(A, knots = seq(15, 65, 10))1     8.548  7.650  9.551
Ns(A, knots = seq(15, 65, 10))2     5.706  4.998  6.514
Ns(A, knots = seq(15, 65, 10))3     1.002  0.890  1.128
Ns(A, knots = seq(15, 65, 10))4    14.402 11.896 17.436
Ns(A, knots = seq(15, 65, 10))5     0.466  0.429  0.505

> aa <- 15:65
> As <- Ns( aa, knots=seq(15,65,10) )
> head( As )

                1 2           3          4           5
[1,] 0.0000000000 0  0.00000000 0.00000000  0.00000000
[2,] 0.0001666667 0 -0.02527011 0.07581034 -0.05054022
[3,] 0.0013333333 0 -0.05003313 0.15009940 -0.10006626
[4,] 0.0045000000 0 -0.07378197 0.22134590 -0.14756393
```


Spline effects in glm

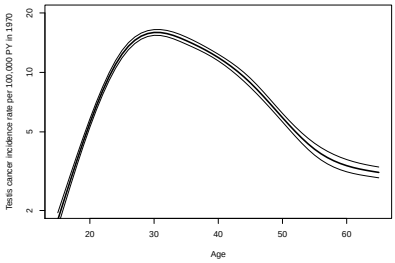



```
> matplot( aa, ci.exp( ms, ctr.mat=cbind(1,As) )*10^5,
+          log="y", xlab="Age", ylab="Testis cancer incidence rate per 100,000 PY"
+          type="l", lty=1, lwd=c(3,1,1), col="black", ylim=c(2,20) )
> matlines( nd$A, ci.exp( mq, ctr.mat=Cq )*10^5,
+           type="l", lty=1, lwd=c(3,1,1), col="blue" )
```


Adding a linear period effect

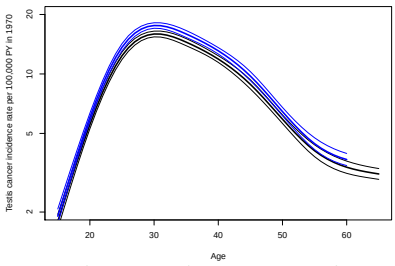
```
> msp <- glm( D ~ Ns(A,knots=seq(15,65,10)) + P,
+                 offset=log(Y), family=poisson, data=testisDK )
> round( ci.lin( msp ), 3 )

                                Estimate StdErr       z     P    2.5%   97.5%
(Intercept)                      -58.105  1.444 -40.229 0.000 -60.935 -55.274
Ns(A, knots = seq(15, 65, 10))1    2.120  0.057  37.444 0.000   2.009   2.231
Ns(A, knots = seq(15, 65, 10))2    1.700  0.068  25.157 0.000   1.567   1.832
Ns(A, knots = seq(15, 65, 10))3    0.007  0.060   0.110 0.913  -0.112   0.125
Ns(A, knots = seq(15, 65, 10))4    2.596  0.097  26.631 0.000   2.405   2.787
Ns(A, knots = seq(15, 65, 10))5   -0.780  0.042 -18.748 0.000  -0.861  -0.698
P                                  0.024  0.001  32.761 0.000   0.023   0.025

> Ca <- cbind( 1, Ns( aa, knots=seq(15,65,10) ), 1970 )
> head( Ca )

                1 2           3          4           5
[1,] 0.0000000000 0  0.00000000 0.00000000  0.00000000 1970
[2,] 0.0001666667 0 -0.02527011 0.07581034 -0.05054022 1970
[3,] 0.0013333333 0 -0.05003313 0.15009940 -0.10006626 1970
[4,] 0.0045000000 0 -0.07378197 0.22134590 -0.14756393 1970
[5,] 0.0106666667 0 -0.09600952 0.28802857 -0.19201905 1970
```


Adding a linear period effect




```
> matplot( aa, ci.exp( msp, ctr.mat=Ca )*10^5,
+          log="y", xlab="Age",
+          ylab="Testis cancer incidence rate per 100,000 PY in 1970",
+          type="l", lty=1, lwd=c(3,1,1), col="black", ylim=c(2,20) )
```


Adding a linear period effect

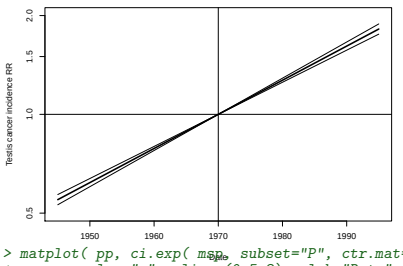



```
> matplot( aa, ci.exp( msp, ctr.mat=Ca )*10^5,
+          log="y", xlab="Age",
+          ylab="Testis cancer incidence rate per 100,000 PY in 1970",
+          type="l", lty=1, lwd=c(3,1,1), col="black", ylim=c(2,20) )
> matlines( nd$A, ci.pred( ms, newdata=nd ),
+           type="l", lty=1, lwd=c(3,1,1), col="blue" )
```


The period effect

```
> round( ci.lin( msp ), 3 )

                                Estimate StdErr       z     P    2.5%   97.5%
(Intercept)                      -58.105  1.444 -40.229 0.000 -60.935 -55.274
Ns(A, knots = seq(15, 65, 10))1    2.120  0.057  37.444 0.000   2.009   2.231
Ns(A, knots = seq(15, 65, 10))2    1.700  0.068  25.157 0.000   1.567   1.832
Ns(A, knots = seq(15, 65, 10))3    0.007  0.060   0.110 0.913  -0.112   0.125
Ns(A, knots = seq(15, 65, 10))4    2.596  0.097  26.631 0.000   2.405   2.787
Ns(A, knots = seq(15, 65, 10))5   -0.780  0.042 -18.748 0.000  -0.861  -0.698
P                                  0.024  0.001  32.761 0.000   0.023   0.025

> pp <- seq(1945,1995,0.2)
> Cp <- cbind( pp ) - 1970
> head( Cp )

     pp
[1,] -25.0
[2,] -24.8
[3,] -24.6
[4,] -24.4
[5,] -24.2
[6,] -24.0
```


Period effect




```
> matplot( pp, ci.exp( msp, subset="P", ctr.mat=Cp ),
+          log="y", ylim=c(0.5,2), xlab="Date",
+          ylab="Testis cancer incidence RR",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
> abline( h=1, v=1970 )
```

A quadratic period effect

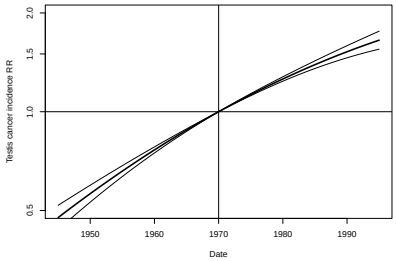
```
> mspq <- glm( D ~ Ns(A,knots=seq(15,65,10)) + P + I(P^2),
+                  offset=log(Y), family=poisson, data=testisDK )
> round( ci.exp( mspq ), 3 )
```

```
                                exp(Est.)   2.5%  97.5%
(Intercept)                         0.000  0.000  0.000
Ns(A, knots = seq(15, 65, 10))1     8.356  7.478  9.337
Ns(A, knots = seq(15, 65, 10))2     5.513  4.829  6.295
Ns(A, knots = seq(15, 65, 10))3     1.006  0.894  1.133
Ns(A, knots = seq(15, 65, 10))4    13.439 11.101 16.269
Ns(A, knots = seq(15, 65, 10))5     0.458  0.422  0.497
P                                   2.189  1.457  3.291
I(P^2)                              1.000  1.000  1.000
```

```
> Cq <- cbind( pp-1970, pp^2-1970^2 )
> head( Cq )
```

```
      [,1]      [,2]
[1,] -25.0 -97875.00
[2,] -24.8 -97096.96
[3,] -24.6 -96318.84
[4,] -24.4 -95540.64
```


A quadratic period effect




```
> matplot( pp, ci.exp( mspq, subset="P", ctr.mat=Cq ),
+          log="y", ylim=c(0.5,2), xlab="Date",
+          ylab="Testis cancer incidence RR",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
> abline( h=1, v=1970 )
```


A spline period effect

Because we have the age-effect with the rate dimension, the period effect is a RR

```
> msps <- glm( D ~ Ns(A,knots=seq(15,65,10)) +
+                  Ns(P,knots=seq(1950,1990,10),ref=1970),
+                  offset=log(Y), family=poisson, data=testisDK )
> round( ci.exp( msps ), 3 )
```

```
                                                exp(Est.)   2.5%  97.5%
(Intercept)                                         0.000  0.000  0.000
Ns(A, knots = seq(15, 65, 10))1                     8.327  7.452  9.305
Ns(A, knots = seq(15, 65, 10))2                     5.528  4.842  6.312
Ns(A, knots = seq(15, 65, 10))3                     1.007  0.894  1.133
Ns(A, knots = seq(15, 65, 10))4                    13.447 11.107 16.279
Ns(A, knots = seq(15, 65, 10))5                     0.458  0.422  0.497
Ns(P, knots = seq(1950, 1990, 10), ref = 1970)1     1.711  1.526  1.918
Ns(P, knots = seq(1950, 1990, 10), ref = 1970)2     2.190  2.028  2.364
Ns(P, knots = seq(1950, 1990, 10), ref = 1970)3     3.222  2.835  3.661
Ns(P, knots = seq(1950, 1990, 10), ref = 1970)4     2.299  2.149  2.459
```


A spline period effect

```
> Cp <- Ns( pp, knots=seq(1950,1990,10),ref=1970)
> head( Cp, 4 )
```

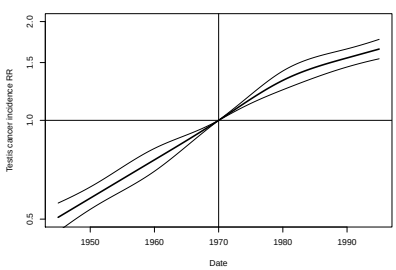
```
             1           2          3         4
[1,] -0.6666667  0.0142689462 -0.5428068 0.3618712
[2,] -0.6666667  0.0091980207 -0.5275941 0.3517294
[3,] -0.6666667  0.0041270951 -0.5123813 0.3415875
[4,] -0.6666667 -0.0009438304 -0.4971685 0.3314457
```

```
> ci.exp( msps, subset="P" )
```

```
                                                exp(Est.)     2.5%    97.5%
Ns(P, knots = seq(1950, 1990, 10), ref = 1970)1  1.710808 1.525946 1.918065
Ns(P, knots = seq(1950, 1990, 10), ref = 1970)2  2.189650 2.027898 2.364303
Ns(P, knots = seq(1950, 1990, 10), ref = 1970)3  3.221563 2.835171 3.660614
Ns(P, knots = seq(1950, 1990, 10), ref = 1970)4  2.298946 2.149148 2.459186
```

```
> matplot( pp, ci.exp( msps, subset="P", ctr.mat=Cp ),
+          log="y", ylim=c(0.5,2), xlab="Date",
+          ylab="Testis cancer incidence RR",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
```


Period effect

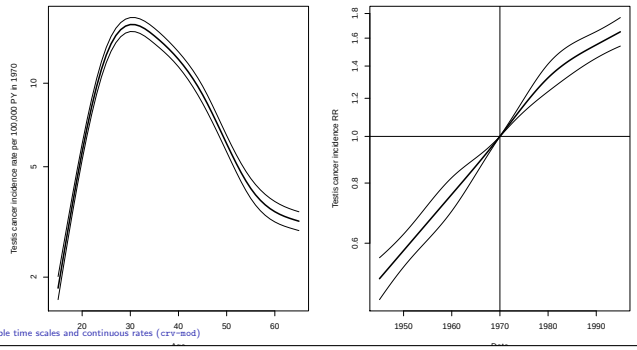



```
> matplot( pp, ci.exp( msps, subset="P", ctr.mat=Cp ),
+          log="y", ylim=c(0.5,2), xlab="Date",
+          ylab="Testis cancer incidence RR",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
> abline( h=1, v=1970 )
```


Period effect

```
> par( mfrow=c(1,2) )
> matplot( aa, ci.pred( msps, newdata=data.frame(A=aa,P=1970,Y=10^5) ),
+          log="y", xlab="Age",
+          ylab="Testis cancer incidence rate per 100,000 PY in 1970",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
> matplot( pp, ci.exp( msps, subset="P", ctr.mat=Cp ),
+          log="y", xlab="Date", ylab="Testis cancer incidence RR",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
> abline( h=1, v=1970 )
```

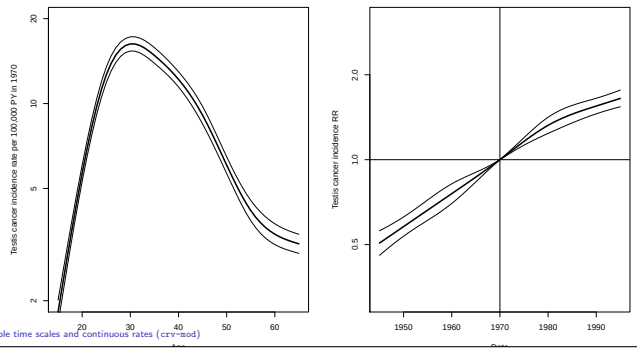

Age and period effect



Period effect

```
> par( mfrow=c(1,2) )
> matplot( aa, ci.pred( msps, newdata=data.frame(A=aa,P=1970,Y=10^5) ),
+          log="y", xlab="Age",
+          ylim=c(2,20), xlim=c(15,65),
+          ylab="Testis cancer incidence rate per 100,000 PY in 1970",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
> matplot( pp, ci.exp( msps, subset="P", ctr.mat=Cp ),
+          log="y", xlab="Date",
+          ylim=c(2,20)/sqrt(2*20), xlim=c(15,65)+1930,
+          ylab="Testis cancer incidence RR",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
> abline( h=1, v=1970 )
```


Age and period effect



Age and period effect with `ci.exp`

- In rate models there is always one term with the **rate** dimension — usually **age**
- But it must refer to a specific **reference** value for **all other** variables (`P`).
- **All** parameters must be used in computing rates, at some reference value(s).
- For the "other" variables, report the RR **relative** to the reference point.
- Only parameters relevant for the variable (`P`) used.
- Contrast matrix is a **difference** between (splines at) the prediction points and the reference point.

Likelihood for multistate follow-up

Bendix Carstensen
Senior Statistician, Steno Diabetes Center

Practice in analysis of multistate models using `Epi::Lexis`
University of Aberdeen,
18 AUgust 2017

`http://BendixCarstensen/AdvCoh/courses/Frias-2016` `ms-lik`

Likelihood for transition through states

$$\mathbf{A} \longrightarrow \mathbf{B} \longrightarrow \mathbf{C} \longrightarrow$$

- given start of observation in **A** at time t_0
- transitions at times t_B and t_C
- survival in **C** till (at least) time t_x:

$$\begin{aligned} L = & \mathrm{P}\{\text{survive } t_0 \to t_B \text{ in } \mathbf{A}\} \\ & \times \mathrm{P}\{\text{transition } \mathbf{A} \to \mathbf{B} \text{ at } t_B \mid \text{alive in } \mathbf{A}\} \\ & \times \mathrm{P}\{\text{survive } t_B \to t_C \text{ in } \mathbf{B} \mid \text{entered } \mathbf{B} \text{ at } t_B\} \\ & \times \mathrm{P}\{\text{transition } \mathbf{B} \to \mathbf{C} \text{ at } t_C \mid \text{alive in } \mathbf{B}\} \\ & \times \mathrm{P}\{\text{survive } t_C \to t_x \text{ in } \mathbf{C} \mid \text{entered } \mathbf{C} \text{ at } t_C\} \end{aligned}$$

- Product of likelihood contributions for each transition
  — each one as for a survival model

Likelihood contributions reflected in `Lexis` object

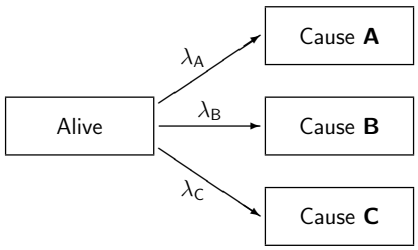
$$\begin{aligned} L = & \mathrm{P}\{\text{survive } t_0 \to t_B \text{ in } \mathbf{A}\} \\ & \times \mathrm{P}\{\text{transition } \mathbf{A} \to \mathbf{B} \text{ at } t_B \mid \text{alive in } \mathbf{A}\} \\ & \times \mathrm{P}\{\text{survive } t_B \to t_C \text{ in } \mathbf{B} \mid \text{entered } \mathbf{B} \text{ at } t_B\} \\ & \times \mathrm{P}\{\text{transition } \mathbf{B} \to \mathbf{C} \text{ at } t_C \mid \text{alive in } \mathbf{B}\} \\ & \times \mathrm{P}\{\text{survive } t_C \to t_x \text{ in } \mathbf{C} \mid \text{entered } \mathbf{C} \text{ at } t_C\} \end{aligned}$$

lex.id	time	lex.dur	lex.Cst	lex.Xst
1	t_0	t_B-t_0	A	B
1	t_B	t_C-t_B	B	C
1	t_C	t_x-t_C	C	C

constant rate in interval ⇒ log-likelihood term is Poisson:
$d\log(\lambda) - \lambda y = (\texttt{lex.Xst}! = \texttt{lex.Cst}) \times \log(\lambda) - \lambda \times \texttt{lex.dur}$

Competing risks

But you may die from more than one cause
(move to one of more possible states):



Cause-specific intensities

$$\begin{aligned} \lambda_A(t) &= \lim_{h\to 0} \frac{\mathrm{P}\{\text{death from cause A in } (t, t+h] \mid \text{alive at } t\}}{h} \\ \lambda_B(t) &= \lim_{h\to 0} \frac{\mathrm{P}\{\text{death from cause B in } (t, t+h] \mid \text{alive at } t\}}{h} \\ \lambda_C(t) &= \lim_{h\to 0} \frac{\mathrm{P}\{\text{death from cause C in } (t, t+h] \mid \text{alive at } t\}}{h} \end{aligned}$$

Total mortality rate:

$$\lambda_{\text{Total}}(t) = \lim_{h\to 0} \frac{\mathrm{P}\{\text{death from any cause in } (t, t+h] \mid \text{alive at } t\}}{h}$$

Cause-specific intensities

For small h, $\mathrm{P}\{2 \text{ events in } (t, t+h]\} \approx 0$, so:

$$\begin{aligned} & \mathrm{P}\{\text{death from any cause in } (t, t+h] \mid \text{alive at } t\} \\ = \; & \mathrm{P}\{\text{death from cause A in } (t, t+h] \mid \text{alive at } t\} + \\ & \mathrm{P}\{\text{death from cause B in } (t, t+h] \mid \text{alive at } t\} + \\ & \mathrm{P}\{\text{death from cause C in } (t, t+h] \mid \text{alive at } t\} \\ \Longrightarrow \quad & \lambda_{\text{Total}}(t) = \lambda_A(t) + \lambda_B(t) + \lambda_C(t) \end{aligned}$$

Intensities are additive,
if they all refer to the
same risk set, in this case "Alive".

Likelihood for competing risks

Data:

Y	-	person years in "Alive"
D_A	-	deaths from cause A
D_B	-	deaths from cause B
D_C	-	deaths from cause C

Now, assume for a start that transition rates between states are constant.

Likelihood for competing risks

A survivor contributes to the log-likelihood:

$$\log(\mathrm{P}\{\text{Survival for a time of } y\}) = -(\lambda_A + \lambda_B + \lambda_C)y$$

A death from cause **A** contributes an additional $\log(\lambda_A)$, from cause **B** an additional $\log(\lambda_B)$ etc.

The total log-likelihood is then:

$$\begin{aligned} \ell(\lambda_A, \lambda_B, \lambda_C) = & D_A \log(\lambda_A) + D_B \log(\lambda_B) + D_C \log(\lambda_C) \\ & - (\lambda_A + \lambda_B + \lambda_C) Y \\ = & [D_A \log(\lambda_A) - \lambda_A Y] + \\ & [D_B \log(\lambda_B) - \lambda_B Y] + \\ & [D_C \log(\lambda_C) - \lambda_C Y] \end{aligned}$$

Components of the likelihood

The log-likelihood is made up of three contributions:

- one for cause A,
- one for cause B and
- one for cause C

Deaths are the cause-specific deaths,

but the **person-years** are the same in all contributions.

The person-years appear once for each transition **out** of a state.

Likelihood for multiple states

- **Product** of likelihoods for each transition
  — each one as for a survival model
- **conditional** on being alive at (observed) entry to current state
- **Risk time** is the risk time in the current ("From", `lex.Cst`) state
- **Events** are transitions to the "To" state (`lex.Xst`)
- All other transitions out of "From" are treated as **censorings** (but they are not)
- Fit models separately for each transition or jointly for all

Time varying rates:

- The same type of analysis as with a constant rates
- . . . but data must be split in intervals sufficiently small to justify an assumption of constant rate (intensity),
- the model should allow for a separate rate for each interval,
- but these can be constrained to follow model with a smooth effect of the time-scale values allocated to each interval.

Practical implications

- Empirical rates ((d, y) from each individual) will be the same for all analyses except for those where deaths occur.
- Analysis of cause **A**:
  - Contributions $(1, y)$ only for those intervals where a cause **A** death occurs.
  - Intervals with cause **B** or **C** deaths (or no deaths) contribute only $(0, y)$ — treated as censorings.

original							expanded				
id	time	cause	xx	d.A	d.B	d.C	id	time	dd	xx	Tr
1	1	B	0.50	0	1	0	1	1	0	0.50	A
2	1	NA	1.00	0	0	0	2	1	0	1.00	A
3	8	B	-1.74	0	1	0	3	8	0	-1.74	A
4	3	A	-0.55	1	0	0	4	3	1	-0.55	A
5	7	NA	-0.58	0	0	0	5	7	0	-0.58	A
6	7	C	-0.04	0	0	1	6	7	0	-0.04	A
							1	1	1	0.50	B
							2	1	0	1.00	B
							3	8	1	-1.74	B
							4	3	0	-0.55	B
							5	7	0	-0.58	B
							6	7	0	-0.04	B
							1	1	0	0.50	C
							2	1	0	1.00	C
							3	8	0	-1.74	C
							4	3	0	-0.55	C
							5	7	0	-0.58	C
							6	7	1	-0.04	C

. . . accomplished by `stack.Lexis`

`Lexis` objects (data frame)

- Represents the **follow-up**
- `lex.dur` contains the total time at risk for (any) event
- `lex.Cst` is the state in which this time is spent
- `lex.Xst` is the state to which a transition occurs — if no transition, the same as `lex.Cst`.

This is used for modelling of single transitions between states — and multiple transitions with no two originating in the same state.

`stacked.Lexis` objects (data frame)

- Represents the **likelihood** contributions
- `lex.dur` contains the total time at risk for (any) event
- `lex.Tr` is the transition to which the record contributes
- `lex.Fail` is the event (failure) indicator for the transition in question.

This is used for joint modelling of **all** transition in a multistate set-up.

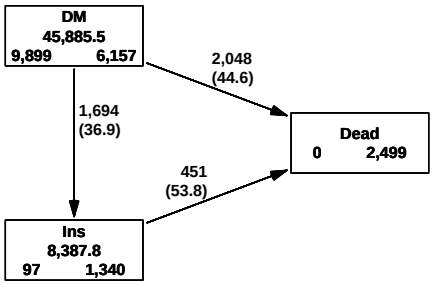
Particularly with several rates originating in the **same** state (competing risks).

Implemented in the `stack.Lexis` function:

```
> library( Epi )
> data(DMlate)
> head(DMlate)

       sex    dobth     dodm    dodth    dooad doins      dox
50185    F 1940.256 1998.917       NA       NA    NA 2009.997
307563   M 1939.218 2003.309       NA 2007.446    NA 2009.997
294104   F 1918.301 2004.552       NA       NA    NA 2009.997
336439   F 1965.225 2009.261       NA       NA    NA 2009.997
245651   M 1932.877 2008.653       NA       NA    NA 2009.997
216824   F 1927.870 2007.886 2009.923       NA    NA 2009.923

> dml <- Lexis( entry = list(Per = dodm,
+                            Age = dodm-dobth,
+                          DMdur = 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.
```


Implemented in the `stack.Lexis` function:

```
> dmi <- cutLexis( dml, cut = dml$doins,
+                  new.state = "Ins",
+                  precursor = "DM" )
> summary( dmi )

Transitions:
     To
From    DM  Ins Dead  Records:  Events: Risk time:  Persons:
  DM  6157 1694 2048      9899     3742   45885.49      9899
  Ins    0 1340  451      1791      451    8387.77      1791
  Sum 6157 3034 2499     11690     4193   54273.27      9996

> boxes( dmi, boxpos = list(x=c(20,20,80),
+                           y=c(80,20,50)),
+            scale.R=1000, show.BE=TRUE, hmult=1.2, wmult=1.1 )
```

Implemented in the `stack.Lexis` function:

```
> options( digits=3, width=200 )
> st.dmi <- stack( dmi )
> print( st.dmi[1:6,], row.names=F )

  Per  Age DMdur lex.dur lex.Cst lex.Xst  lex.Tr lex.Fail lex.id sex dobth dodm do
 1999 58.7     0  11.080      DM      DM DM->Ins    FALSE      1   F  1940 1999
 2003 64.1     0   6.689      DM      DM DM->Ins    FALSE      2   M  1939 2003
 2005 86.3     0   5.446      DM      DM DM->Ins    FALSE      3   F  1918 2005
 2009 44.0     0   0.736      DM      DM DM->Ins    FALSE      4   F  1965 2009
 2009 75.8     0   1.344      DM      DM DM->Ins    FALSE      5   M  1933 2009
 2008 80.0     0   2.037      DM    Dead DM->Ins    FALSE      6   F  1928 2008  1

> str( st.dmi )

Classes 'stacked.Lexis' and 'data.frame': 21589 obs. of  16 variables:
 $ Per     : num  1999 2003 2005 2009 2009 ...
 $ Age     : num  58.7 64.1 86.3 44 75.8 ...
 $ DMdur   : num  0 0 0 0 0 0 0 0 0 0 ...
 $ lex.dur : num  11.08 6.689 5.446 0.736 1.344 ...
 $ lex.Cst : Factor w/ 3 levels "DM","Ins","Dead": 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Xst : Factor w/ 3 levels "DM","Ins","Dead": 1 1 1 1 1 3 1 1 3 1 ...
 $ lex.Tr  : Factor w/ 3 levels "DM->Ins","DM->Dead",..: 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Fail: logi  FALSE FALSE FALSE FALSE FALSE FALSE ...
```


Implemented in the `stack.Lexis` function:

```
> print( subset(    dmi, lex.id %in% c(13,15,28) ), row.names=FALSE )

  Per  Age DMdur lex.dur lex.Cst lex.Xst lex.id sex dobth dodm dodth dooad doins
 1997 59.4   0.0   0.890      DM    Dead     13   M  1938 1997  1998    NA    NA 1
 2003 58.1   0.0   2.804      DM     Ins     15   M  1944 2003    NA    NA  2005 2
 2005 60.9   2.8   4.643     Ins     Ins     15   M  1944 2003    NA    NA  2005 2
 1999 73.7   0.0   8.701      DM     Ins     28   F  1925 1999  2008  2001  2007 2
 2007 82.4   8.7   0.977     Ins    Dead     28   F  1925 1999  2008  2001  2007 2

> print( subset( st.dmi, lex.id %in% c(13,15,28) ), row.names=FALSE )

  Per  Age DMdur lex.dur lex.Cst lex.Xst    lex.Tr lex.Fail lex.id sex dobth dodm
 1997 59.4   0.0   0.890      DM    Dead   DM->Ins    FALSE     13   M  1938 1997
 2003 58.1   0.0   2.804      DM     Ins   DM->Ins     TRUE     15   M  1944 2003
 1999 73.7   0.0   8.701      DM     Ins   DM->Ins     TRUE     28   F  1925 1999
 1997 59.4   0.0   0.890      DM    Dead  DM->Dead     TRUE     13   M  1938 1997
 2003 58.1   0.0   2.804      DM     Ins  DM->Dead    FALSE     15   M  1944 2003
 1999 73.7   0.0   8.701      DM     Ins  DM->Dead    FALSE     28   F  1925 1999
 2005 60.9   2.8   4.643     Ins     Ins Ins->Dead    FALSE     15   M  1944 2003
 2007 82.4   8.7   0.977     Ins    Dead Ins->Dead     TRUE     28   F  1925 1999
```

Analysis of rates in multistate models

- Interactions between all covariates (including time) and state (`lex.Cst`):
  $\Leftrightarrow$ separate analyses of all transition rates.
- Only interaction between state (`lex.Cst`) and time(scales):
  $\Leftrightarrow$ same covariate effects for all causes transitions, but separate baseline hazards — "stratified model".
- Main effect of state only (`lex.Cst`):
  $\Leftrightarrow$ proportional hazards
- No effect of state:
  $\Leftrightarrow$ identical baseline hazards — hardly ever relevant.

Analysis approaches and data representation

- `Lexis` objects represents the precise follow-up in the cohort, in states and along timescales
- — used for analysis of single transition rates.
- `stacked.Lexis` objects represents contributions to the total likelihood
- — used for joint analysis of (all) rates in a multistate setup
- . . . which is the case if you want to specify common effects between different transitions.

Assumptions in competing risks

"Classical" way of looking at survival data:
description of the distribution of time to death.

For competing risks that would require three variables:
T_A, T_B and T_C, representing times to death from each of the three causes.
But at most one of these is observed.

Often it is stated that these must be assumed independent in order to make the likelihood machinery work

1. It is not necessary.
2. Independence can never be assessed from data.

An account of these problems is given in:

PK Andersen, SZ Abildstrøm & S Rosthøj:
Competing risks as a multistate model,
Statistical Methods in Medical Research; **11**, 2002: pp. 203–215

Per Kragh Andersen, Ronald B Geskus, Theo de Witte & Hein Putter:
Competing risks in epidemiology: possibilities and pitfalls,
International Journal of Epidemiology; 2012: pp. 1–10

Contains examples where both dependent and independent "cause specific survival times" gives rise to the same set of cause specific rates.

Lifetime risk

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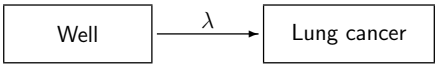
Practice in analysis of multistate models using `Epi::Lexis`
University of Aberdeen,
18 AUgust 2017

`http://BendixCarstensen/AdvCoh/courses/Frias-2016` DK-lung

Competing risk interpretation

The problems with competing risk models **only** comes when estimated intensities (rates) are used to produce probability statements.

Classical set-up in cancer-registries:

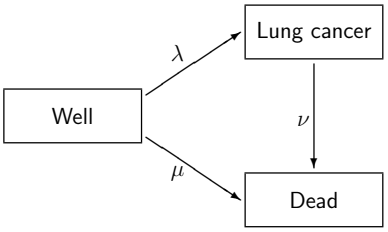


Common statement:

$$\mathrm{P}\left\{\text{Lung cancer before age 75}\right\} = 1 - \mathrm{e}^{-\Lambda(75)}$$

This is not quite right.

How the world really looks



Illness-death model, mortality of lung cancer patients (ν) not relevant here, we only want to find out how many pass through "Lung cancer"

How many get lung cancer before age a?

$$\mathrm{P}\left\{\text{Lung cancer before age 75}\right\} \neq 1 - \mathrm{e}^{-\Lambda(75)}$$

the r.h.s. does not take the possibility of death prior to lung cancer into account.

- $1 - \mathrm{e}^{-\Lambda(75)}$ often stated as the probability of lung cancer before age 75, assuming all other acuses of death absent.
- Lung cancer rates are however observed in a mortal population.
- If all other causes of death were absent, this would assume that lung cancer rates remained the same.

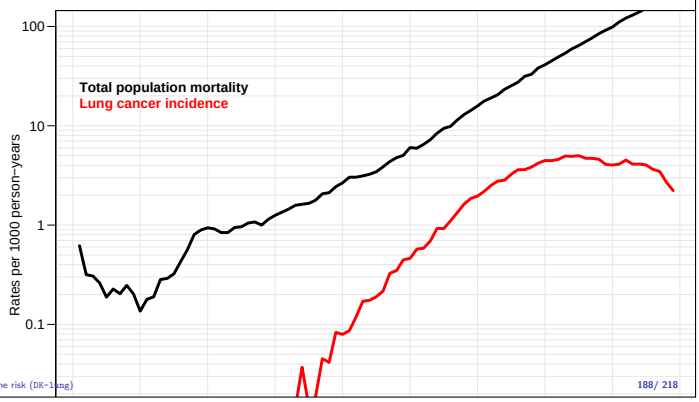
How it really is:

$$\begin{aligned}
&\mathrm{P}\left\{\text{Lung cancer diagnosis before age } a\right\} \\
&= \int_0^a \mathrm{P}\left\{\text{Lung cancer at age } u\right\}\,\mathrm{d}u \\
&= \int_0^a \mathrm{P}\left\{\text{Lung cancer in age } (u, u+\mathrm{d}u] \mid \text{alive at } u\right\} \\
&\qquad \times \mathrm{P}\left\{\text{alive at } u \text{ without lung cancer}\right\}\,\mathrm{d}u \\
&= \int_0^a \lambda(u)\exp\left(-\int_0^u \mu(s)+\lambda(s)\,\mathrm{d}s\right)\,\mathrm{d}u
\end{aligned}$$

Probability of lungcancer

The rates are easily plotted for inspection in R:

```
matplot( age, 1000*cbind( D/Y, lung/Y ),
         log="y", type="l", lty=1, lwd=3,
         ylim=c(0.01,100), xlab="Age",
         ylab="Rates per 1000 person-years" )
```



Life expectancy and life lost

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University of Aberdeen,
18 AUgust 2017

`http://BendixCarstensen/AdvCoh/courses/Frias-2016` `lifelost`

The probablility that a person contracts lung cancer before age a is:

$$\int_0^a \lambda(u) \exp\left(-\int_0^u \mu(s)+\lambda(s)\,\mathrm{d}s\right)\,\mathrm{d}u$$

$$= \int_0^a \lambda(u) \exp\Big(-\big(\mathrm{M}(u)+\Lambda(u)\big)\Big)\,\mathrm{d}u$$

$\mathrm{M}(u)$ is the cumulative mortality rate.

$\Lambda(u)$ is the cumulative lung cancer incidence rate.

Life expectancy

The expected lifetime (at birth) is the variable age (a) integrated with respect to the distribution of age at death:

$$\mathrm{EL} = \int_0^\infty a f(a)\,\mathrm{d}a$$

where f is the density of the distribution of lifetimes.

Simplest computed as the area under the survival curve:

$$\mathrm{EL} = \int_0^\infty S(a)\,\mathrm{d}a$$

R-commands needed to do the calculations:

```
cr.death <- cumsum( D/Y )
cr.lung <- cumsum( lung/Y )
p.simple <- 1 - exp( -cr.lung )
p.lung <- cumsum( lung/Y *
                  exp( -(cr.death+cr.lung) ) )
matlines( age, 100*cbind( cr.lung, p.simple, p.lung ),
          type="l", lty=1, lwd=2*c(2,2,3),
          col=c("black","blue","red") )
```


Life expectancy at age a

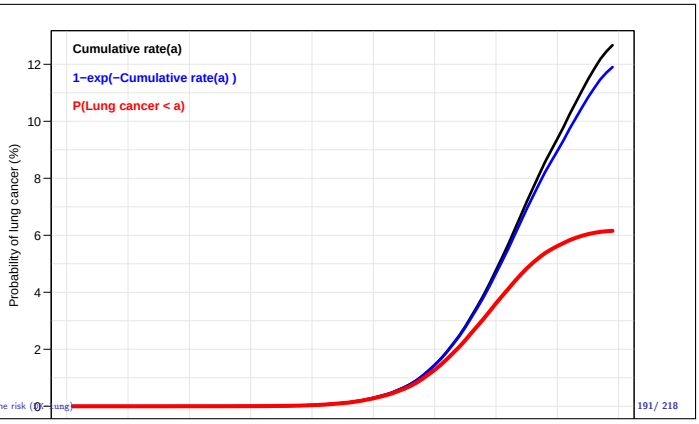
Use the **conditional** survival function, given alive at age a

$$\mathrm{P}(\text{Survive till } t|\text{alive at } a) = S(t)/S(a)$$

Life expectancy at age a:

$$\mathrm{EL}(a) = \int_a^\infty S(t)/S(a)\,\mathrm{d}t$$

— the area under the conditional survival function.



Lifetime lost

— due to a disease is the **difference** between the expected residual lifetime for a diseased person and a non-diseased (well) person at the same age:

$$\mathrm{LL}(a) = \int_a^\infty S_{\text{Well}}(u)/S_{\text{Well}}(a) - S_{\text{Diseased}}(u)/S_{\text{Diseased}}(a)\,\mathrm{d}u$$

Note that the survival for a "well" person, $S_{\text{Well}}(a)$ must be defined:

- includes the possibility to become diseased (increase mortality)
- **or** assumes immunity to the disease

Assumptions

- The calculation and the statement "6% of Danish males will get lung cancer" assumess that the lung cancer rates and the mortality rates in the file apply to a cohort of men.
- But they are cross-sectional rates, so the assumption is one of steady state of:
  1. mortality rates (which is dubious)
  2. lung cancer incidence rates (which is appalling).
- However, the machinery can be applied to any set of rates for competing risks, regardless of how they were estimated.

Lifetime lost using rates

- age-specific mortality rates $\lambda(a)$
- survival function $S(a) = \exp(-\int_0^a \lambda(u)\,\mathrm{d}u)$
- residual lifetime $\mathrm{EL}(a) = \int_a^\infty S(u)\,\mathrm{d}u)$
- do for "well" and "dis"
- life lost at age a: $\mathrm{LL}(a) = \mathrm{EL}_{\text{well}}(a) - \mathrm{EL}_{\text{dis}}(a)$

Lifetime lost in practice

- Compute mortality rates at age midpoints of small intervals (1/10 year long, say):
  0.05, 0.15, 0.25, ... — $\lambda(a)$, `lambda`
- Compute the integral by summing $\lambda(a) \times 0.1$
  `cumsum(lambda*0.1)` — $\Lambda(a)$
- Compute survival function as $\exp$ of minus this `S <- exp(-cumsum(lambda*0.1))`
- Expected life time at age 40, say, is then the integral of the conditionl survival: `sum(S[400:1000]/S[400])*0.1`
- Compute both for well and dis, and subtract.
- — now you do the practical...

Reporting a multistate model

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18 AUgust 2017

`http://BendixCarstensen/AdvCoh/courses/Frias-2016` ms-rep

Multistate models

- Outcomes are transitions between states, with times
- Covariates are measurements and timescales
- Models describe the single transition rates
- Results are:
  - Description of rates — how do they depend time etc.
  - Prediction of state occupancy:
    What is the probability that a person is in a given state at a given time?
- This illustrates the latter.

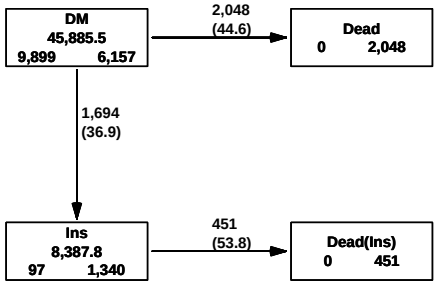
Diabetes patient mortality

```
> library(Epi)
> data(DMlate)
> dml <- Lexis( entry = list(Per=dodm, Age=dodm-dobth, DMdur=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.

> summary(dml)

Transitions:
     To
From   DM Dead  Records:  Events: Risk time:  Persons:
  DM 7497 2499      9996     2499   54273.27      9996
```


... subdivided by insulin status

Split follow-up at insulin, introduce a new timescale and split non-precursor states:

```
> dmi <- cutLexis( dml, cut = dml$doins,
+                       pre = "DM",
+                 new.state = "Ins",
+                 new.scale = "t.Ins",
+               split.states = TRUE )
> summary( dmi )

Transitions:
     To
From    DM  Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM  6157 1694 2048         0      9899     3742   45885.49      9899
  Ins    0 1340    0       451      1791      451    8387.77      1791
  Sum 6157 3034 2048       451     11690     4193   54273.27      9996

> boxes( dmi, boxpos=list(x=c(20,20,80,80),y=c(80,20,80,20)),
+             scale.R=1000, show.BE=TRUE, hmult=1.2, wmult=1.2 )
```

Split the follow in 3-month intervals for modelling

```
> Si <- splitLexis( dmi, 0:60/4, "DMdur" )
> summary( Si )

Transitions:
     To
From      DM   Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM  184986  1694 2048         0    188728     3742   45885.49      9899
  Ins      0 34707    0       451     35158      451    8387.77      1791
  Sum 184986 36401 2048       451    223886     4193   54273.27      9996

> summary( dmi )

Transitions:
     To
From    DM  Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM  6157 1694 2048         0      9899     3742   45885.49      9899
  Ins    0 1340    0       451      1791      451    8387.77      1791
  Sum 6157 3034 2048       451     11690     4193   54273.27      9996
```


Define knots for spline modelling of the rates:

```
> nk <- 4
> ( ai.kn <- with( subset(Si,lex.Xst=="Ins"),
+                  quantile( Age+lex.dur, probs=(1:nk-0.5)/nk ) ) )
   12.5%    37.5%    62.5%    87.5%
27.68241 49.61893 61.88364 75.56211

> ( ad.kn <- with( subset(Si,lex.Xst=="Dead"),
+                  quantile( Age+lex.dur, probs=(1:nk-0.5)/nk ) ) )
   12.5%    37.5%    62.5%    87.5%
63.61875 74.98700 81.38501 89.26831

> ( di.kn <- with( subset(Si,lex.Xst=="Ins"),
+                  quantile( DMdur+lex.dur, probs=(1:nk-0.5)/nk ) ) )
12.5% 37.5% 62.5% 87.5%
 1.50  4.25  7.00 10.50

> ( dd.kn <- with( subset(Si,lex.Xst=="Dead"),
+                  quantile( DMdur+lex.dur, probs=(1:nk-0.5)/nk ) ) )
     12.5%      37.5%      62.5%      87.5%
0.3778234 1.9582478 4.3370979 8.0232717
```


Fit Poisson models to transition rates

```
> DM.Ins <- glm( (lex.Xst=="Ins") ~ Ns( Age   , knots=ai.kn ) +
+                                   Ns( DMdur, knots=di.kn ) +
+                                   I(Per-2000) + sex,
+                family=poisson, offset=log(lex.dur),
+                data = subset(Si,lex.Cst=="DM") )
> DM.Dead <- glm( (lex.Xst=="Dead") ~ Ns( Age   , knots=ad.kn ) +
+                                    Ns( DMdur, knots=dd.kn ) +
+                                    I(Per-2000) + sex,
+                 family=poisson, offset=log(lex.dur),
+                 data = subset(Si,lex.Cst=="DM") )
> Ins.Dead <- glm( (lex.Xst=="Dead(Ins)") ~ Ns( Age   , knots=ad.kn ) +
+                                           Ns( DMdur, knots=dd.kn ) +
+                                           Ns( t.Ins, knots=td.kn ) +
+                                           I(Per-2000) + sex,
+                  family=poisson, offset=log(lex.dur),
+                  data = subset(Si,lex.Cst=="Ins") )
```


Put the fitted models into an object representing the transitions

```
> Tr <- list( "DM" = list( "Ins"       = DM.Ins,
+                          "Dead"      = DM.Dead  ),
+             "Ins" = list( "Dead(Ins)" = Ins.Dead ) )
> lapply( Tr, names )

$DM
[1] "Ins"  "Dead"

$Ins
[1] "Dead(Ins)"
```

Define an initial object
— note the combination of `select=` and `NULL` which ensures that the relevant attributes from the Lexis object `Si` are carried over to `ini` (using `Si[NULL,1:9]` will lose essential attributes)

```
> ini <- subset(Si,select=1:9)[NULL,]
> ini[1:2,"lex.Cst"] <- "DM"
> ini[1:2,"Per"] <- 1995
> ini[1:2,"Age"] <- 60
> ini[1:2,"DMdur"] <- 5
> ini[1:2,"sex"] <- c("M","F")
> ini

  lex.id  Per Age DMdur t.Ins lex.dur lex.Cst lex.Xst sex
1     NA 1995  60     5    NA      NA      DM    <NA>   M
2     NA 1995  60     5    NA      NA      DM    <NA>   F
```


Simulate 10,000 of each sex using the estimated models in `Tr`:

```
> system.time(
+ simL <- simLexis( Tr, ini, time.pts=seq(0,11,0.5), N=10000 ) )

   user  system elapsed
 24.330   0.040  24.365

> summary( simL )

Transitions:
     To
From     DM   Ins Dead Dead(Ins)  Records:  Events: Risk time:  Persons:
  DM   8831  6057 5112          0     20000    11169  149966.28     20000
  Ins     0  4389    0       1668      6057     1668   33293.03      6057
  Sum  8831 10446 5112       1668     26057    12837  183259.32     20000

> subset( simL, lex.id < 3 )

  lex.id      Per      Age    DMdur t.Ins   lex.dur lex.Cst   lex.Xst sex cens
1      1 1995.000 60.00000 5.000000    NA 10.989503      DM      Dead   M 2006
2      2 1995.000 60.00000 5.000000    NA  3.517961      DM       Ins   M 2006
3      2 1998.518 63.51796 8.517961     0  3.346653     Ins Dead(Ins)   M 2006
```

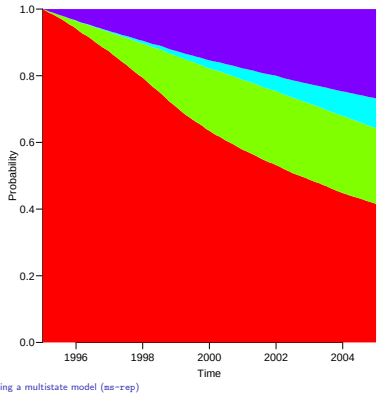

We now have a dataframe (`Lexis` object) with simulated follow-up of 10,000 men and 10,000 women.

We then find the number of persons in each state at a specified set of times.

```
> nSt <- nState( subset(simL,sex=="M"),
+                at=seq(0,10,0.1), from=1995, time.scale="Per" )
> nSt

        State
when         DM   Ins  Dead Dead(Ins)
  1995    10000     0     0          0
  1995.1   9942    24    34          0
  1995.2   9885    39    76          0
  1995.3   9844    52   104          0
  1995.4   9788    69   143          0
  1995.5   9732    91   176          1
  1995.6   9674   114   208          4
  1995.7   9608   144   242          6
  1995.8   9537   174   281          8
  1995.9   9485   194   310         11
  1996     9416   231   340         13
```

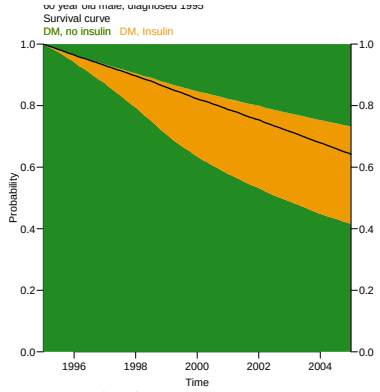

Show the cumulative prevalences in a different order than that of the state-level ordering and plot them using all defaults:

```
> pp <- pState( nSt, perm=c(1,2,4,3) )
> head( pp )

        State
when         DM    Ins Dead(Ins) Dead
  1995   1.0000 1.0000    1.0000    1
  1995.1 0.9942 0.9966    0.9966    1
  1995.2 0.9885 0.9924    0.9924    1
  1995.3 0.9844 0.9896    0.9896    1
  1995.4 0.9788 0.9857    0.9857    1
  1995.5 0.9732 0.9823    0.9824    1

> plot( pp )
```

We can show the results in an clearer way, buy choosing colors wiser:

```
> clr <- c("orange2","forestgreen")
> par( las=1, mar=c(3,3,3,3) )
> plot( pp, col=clr[c(2,1,1,2)] )
> lines( as.numeric(rownames(pp)), pp[,2], lwd=2 )
> mtext( "60 year old male, diagnosed 1995", side=3, line=2.5, adj=0 )
> mtext( "Survival curve", side=3, line=1.5, adj=0 )
> mtext( "DM, no insulin   DM, Insulin", side=3, line=0.5, adj=0, col=clr[1] )
> mtext( "DM, no insulin", side=3, line=0.5, adj=0, col=clr[2] )
> axis( side=4 )
```

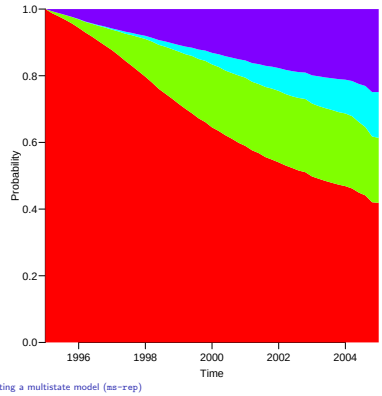
We could also use a Cox-model for the mortality rates assuming the two mortality rates to be proportional:

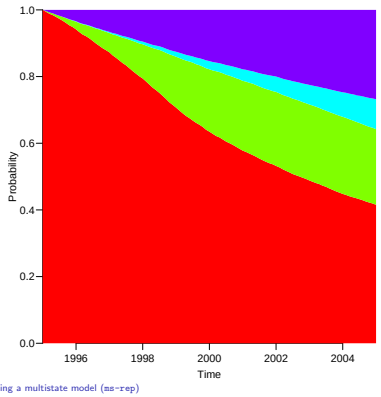
When we fit a Cox-model, `lex.dur` must be used in the `Surv()` function, and the `I()` construction must be used when specifying intermediate states as covariates, since factors with levels not present in the data will create `NA`s in the parameter vector returned by `coxph`, which in return will crash the simulation machinery.

```
> library( survival )
> Cox.Dead <- coxph( Surv( DMdur, DMdur+lex.dur,
+                          lex.Xst %in% c("Dead(Ins)","Dead")) ~
+                    Ns( Age-DMdur, knots=ad.kn ) +
+                    I(lex.Cst=="Ins") +
+                    I(Per-2000) + sex,
+                data = Si )
```



```
> Cr <- list( "DM" = list( "Ins"       = DM.Ins,
+                          "Dead"      = Cox.Dead  ),
+             "Ins" = list( "Dead(Ins)" = Cox.Dead ) )
> simL <- simLexis( Cr, ini, time.pts=seq(0,11,0.2), N=10000 )
> nSt <- nState( subset(simL,sex=="M"),
+                at=seq(0,10,0.2), from=1995, time.scale="Per" )
> pp <- pState( nSt, perm=c(1,2,4,3) )
> plot( pp )
```



References

Now your turn. . .