

# History and Ecology of R

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SPE 2019, Tartu



## Pre-history

*Before there was R, there was S.*



## The S language

Developed at AT&T Bell laboratories by Rick Becker, John Chambers, Doug Dunn, Paul Tukey, Graham Wilkinson.

Version 1	1976–1980	Honeywell GCOS, Fortran-based
Version 2	1980–1988	Unix; Macros, Interface Language
	1981–1986	QPE (Quantitative Programming Environment)
	1984–	General outside licensing; books
Version 3	1988–1998	C-based; S functions and objects
	1991–	Statistical models; informal classes and methods
Version 4	1998	Formal class-method model; connections; large objects
	1991–	Interfaces to Java, Corba?

Source: Stages in the Evolution of S <http://ect.bell-labs.com/sl/S/history.html>







## S-PLUS

- AT&T was a regulated monopoly with limited ability to exploit creations of Bell Labs.
- S source code was supplied for free to universities
- After the break up of AT&T in 1984 it became possible for them to sell S.
- S-PLUS was a commercially available form of S licensed to Statistical Sciences (later Mathsoft, later Insightful) with added features:
  - GUI, survival analysis, non-linear mixed effects, Trellis graphics, ...

Navigation icons: back, forward, search, etc.



## The Rise and Fall of S-PLUS

- 1988. Statistical Science releases first version of S-PLUS.
- 1993. Acquires exclusive license to distribute S. Merges with Mathsoft.
- 2001. Changes name to Insightful.
- 2004. Purchases S language for \$2 million.
- 2008. Insightful sold to TIBCO. S-PLUS incorporated into TIBCO Spotfire.

Navigation icons: back, forward, search, etc.



## History

*How R started, and how it turned into an S clone*

Navigation icons: back, forward, search, etc.







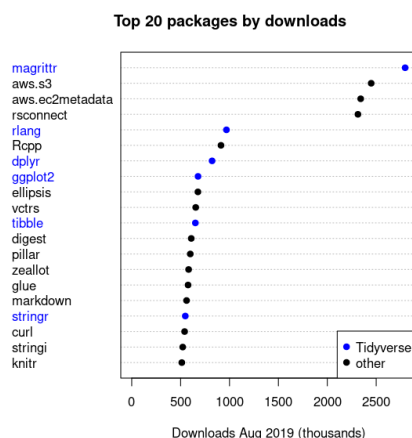
## The present

The current era is characterized by

- A mature R community
- Large penetration of R in the commercial world (“data science”, “analytics”, “big data”)
- Increasing interest in the R language from computer scientists.



- useR! Annual conference
  - Toulouse (2019), Saint Louis (2020)
- R Journal (<http://journal.r-project.org>)
  - Journal of record, peer-reviewed articles, indexed
  - Journal of Statistical Software (JSS) has many articles dedicated to R packages (<http://jstatsoft.org>)
- Migration to social media
  - Stack Exchange/Overflow, Github, Twitter (#rstats)
  - Follow @R.Foundation on Twitter





- *R: Regulatory Compliance and Validation Issues* guidance document by The R Foundation
- ValidR by Mango Solutions
- MRAN (<https://mran.microsoft.com/>), a time-stamped version of CRAN
  - Allows analysis to be re-run with exactly the same package versions at a later date.
  - Used by Microsoft R Open, Microsoft's distribution of R.

Name	Language	Commercial sponsor	Open source	Ongoing
pqR	C		Yes	Yes
CXXR/rho	C++	Google	Yes	No
ORBIT	C	Huawei	Yes	No
Renjin	Java	BeDataDriven	Yes	Yes
FastR	Java	Oracle	Yes	Yes
Riposte	C++	Tableau Research	Yes	No
TERR	C++	TIBCO	No	Yes

A number of projects have looked improving the efficiency of R, either by forking the original codebase or by re-implementing R.

A non-profit organization working in the public interest, founded in 2002 in order to:

- Provide support for the R project and other innovations in statistical computing.
- Provide a reference point for individuals, institutions or commercial enterprises that want to support or interact with the R development community.
- Hold and administer the copyright of R software and documentation (This never happened)





In 2015, a group of organizations created a consortium to support the R ecosystem.

Current members (August 2019)

**R Foundation** A statutory member of The R Consortium

**Platinum members** Microsoft, Moore Foundation, RStudio

**Gold members** TIBCO, Genentech

**Silver members** Alteryx, DataCamp, Esri, Google, Mango Solutions, Oracle, ProCogia



*"Prediction is very difficult, especially about the future" – variously attributed to Niels Bohr, Piet Hein, Yogi Bera*



We cannot make predictions, but some long-term trends are very visible:

- Average age of R Core Team?
- Younger R developers more closely associated with industry than academia
- R Consortium provides mechanism for substantial investment in R infrastructure

## What does all of this mean for the course?

- R incorporates over 40 years of ideas in statistical computing from multiple contributors.
- There is usually more than one way to do something in R.
- Some of the peculiarities of the R language are there for historical reasons.
- The course does not cover some of the recent additions to the R ecosystem.

## Resources

- Chambers J, Stages in the Evolution of S
- Becker, R, A Brief History of S
- Chambers R, Evolution of the S language
- Ihaka, R and Gentleman R, R: A language for Data Analysis and Graphics, *J Comp Graph Stat*, **5**, 299–314, 1996.
- Ihaka, R, R: Past and Future History, Interface 98.
- Ihaka, R, Temple Lang, D, Back to the Future: Lisp as a Base for a Statistical Computing System
- Fox, J, Aspects of the Social Organization and Trajectory of the R Project, *R Journal*, Vol 1/2, 5–13, 2009.

## R: language and basic data management

Krista Fischer

Statistical Practice in Epidemiology, Tartu, 2019  
(initial slides by P. Dalgaard)

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### Language

- ▶ R is a programming language – also on the command line
- ▶ (This means that there are *syntax rules*)

On the command line (or a line in a script) one could:

- ▶ Print an object by typing its name
- ▶ Evaluate an expression
- ▶ Call a function, giving the arguments in parentheses – possibly empty
- ▶ Notice `objects` vs. `objects()`

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### 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

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## R expressions

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m <- mean(x)
sum((x - m)^2)
  
```

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- ▶ Explicit constants
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- ▶ Assignment of results to names

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## R expressions

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- ▶ Arithmetic operators
- ▶ **Function calls**
- ▶ Assignment of results to names

## R expressions

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

## Objects

- ▶ The simplest object type is *vector*
- ▶ Modes: numeric, character, factor, ...
- ▶ 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

## Example (numeric vectors)

```
> a <- c(2, 8, 3, 1, 0, 7)
> b <- c(3, 4, 1, 4, 5, 2)
> a+b
[1] 5 12 4 5 5 9
> mean(a)
[1] 3.5
> m <- mean(a)
> m
[1] 3.5
> a - m # notice recycling
[1] -1.5 4.5 -0.5 -2.5 -3.5 3.5

> z <- c(1, 2, 3)
> a - z #recycling!
[1] 1 6 0 0 -2 4
```

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## Factors

- **Factors** are used to describe groupings – these are just integer codes plus a set of names, as labels for the *levels*
- In model specifications, a factor variable is treated as a classification rather than as a quantitative variable

Example:

```
> x<-c(1,3,3,2,1,3,1)
> fx<-factor(x,labels=c("bad","average","good"))

> fx
[1] bad      good      good      average bad      good

> levels(fx)
[1] "bad"      "average" "good"
```

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## Lists

- Lists are vectors where the elements can have different types – thus collections of any elements, gathered into one object
- Functions often return lists
- `lst <- list(A=rnorm(5), B="hello")`
- Special indexing:
  - `lst$A`
  - `lst[[1]]` first element (NB: double brackets)
- **Data frames** are special type of lists

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## Matrices

- ▶ A **matrix** is a rectangular collection of data. All columns of a matrix should be of the same type.

```
> A<-matrix(c(1,4,2,6,7,8),nrow=3,ncol=2,
              byrow=T)
```

```
> A
      [,1] [,2]
[1,]     1     4
[2,]     2     6
[3,]     7     8
```

- ▶ One 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`.

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## Data frames

- ▶ Usually a dataset in R is stored in a form of a **data frame**.
- ▶ While reading in data from text files (using `read.table()`, `read.csv()`), a data frame is created.
- ▶ A data frame is similar to a matrix, but can have columns (variables) of different types.
- ▶ A variable can be extracted using `dataframe$variable` (as data frames are lists)

```
> D<- data.frame(a=c(8,3,5),b=c("X","Z","Y"))
> D
  a b
1 8 X
2 3 Z
3 5 Y
> D$a
[1] 8 3 5
```

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## Matrices or data frames?

- ▶ A (numeric or character) matrix can be converted to a data frame and vice versa (with `as.data.frame(A)` and `as.matrix(B)`).
- ▶ Most R functions for statistical analysis work with data frames, but in some cases it is useful to have a matrix (incl the occasions where you want to use some matrix algebra).
- ▶ If you need more dimensions than two, there is also `array`.

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## How to access variables in the data frame?

Different ways to tell R to use variable X from data frame D:

- ▶ As mentioned, you can use the `dataframe$variable` notation  
`summary(D$X)`
- ▶ Use the `with` function  
`with(D, summary(X))`
- ▶ Use the `data` argument (does not work for all functions)  
`lm(Y~X, data=D)`
- ▶ Attach the dataframe – **DISCOURAGED!**  
 (seems a convenient solution, but can actually make things more complicated, as it creates a temporary copy of the dataset)  
`attach(D)`  
`summary(X)`  
`detach()`

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## Data manipulation

To create a new variable `bmi` in the existing data frame `students`, use either of the two:

```
students$bmi <-
  with(students, weight/(height/100)^2)
students <-
  transform(students, bmi=weight/(height/100)^2)
```

(notice: you need an assignment, to save the transformed object)

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## Indexing – extracting elements from objects

**Square brackets [ ] are used for indexing!**

Examples:

- ▶ Elements of vectors: `a[5]` (5th element); `a[5:7]` (5th to 7th elements); `a[-6]` (all elements except the 6th)
- ▶ Logical index: `a[a<3]`, `a[b>2]`, `a[is.na(b)]`  
 (elements of `a` corresponding to missing values of `b`)
- ▶ In a data frame or matrix – two dimensions, two indexes:  
`students[5, 7]`, `students[1:10, c(2,5)]`,  
`students[1, ]`, `students[, 3]` (entire row/column)

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## Examples of indexing

```
> x<- c(2,7,3,1,5,9,0)
> x[c(1,5,7)]
[1] 2 5 0
> x[x<3]
[1] 2 1 0

> NMRimp[1:2,1:4] #quick look at a large data
sample.id XXL.VLDL.P XXL.VLDL.L XXL.VLDL.PL
1 V18566 1.46e-04 0.0313 0.00331
2 V36115 9.00e-05 0.0195 0.00178

> fgsa[is.na(fgsa$height),"age"]
[1] 18 69 52 41 52 44 73 28 66 20 73 63 26
# ages of those with missing height

# equivalent: fgsa$age[is.na(fgsa$height)]
```

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## Naming

- Elements of vectors, rows and columns of matrices and data frames can have names
 

```
> x <- c(boys=1.2, girls=1.1)
> x
  boys girls
  1.2   1.1
> x["boys"]
boys
  1.2
> D[, "a"] # works for matrices and data frames
[1] 8 3 5
```
- You can extract and set names with `names(x)`; for matrices and data frames also `colnames(x)` and `rownames(x)`;

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## 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

```
> summary(x) # a numeric vector
Min. 1st Qu. Median Mean 3rd Qu. Max.
 1      1      2      2      3      3

> summary(fx) # a factor
bad average good
 3      1      3
```

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```

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

```

- ▶ Names of 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.
- ▶ Quite often – first argument is not named, but the others are named

## Example

```
t.test(x, y = NULL,
       alternative = c("two.sided", "less", "greater"),
       mu = 0, paired = FALSE, var.equal = FALSE,
       conf.level = 0.95, ...)
```

- ▶ The first argument (x) does not have a default – you have to provide some data!
- ▶ The other arguments can be modified, if you need to.

## Example (cont.)

```
t.test(a, b, alternative="less", paired=TRUE)
t.test(a, b, paired=TRUE, alt="less")

t.test(a, b, p=T, a="l")    #not a good style!
```

Partial keyword matching is possible ("alternative" or "alt" or "a")  
(partial matching is possible)

For a readable code, the use of explicit argument names is highly recommended!

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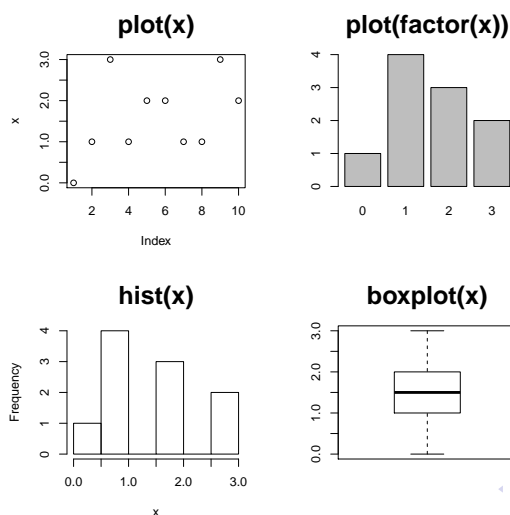
## Basic graphics

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
- ▶ Similarly, the `plot(x, y)` produces a scatter plot, when  $x$  is a numeric variable and a bar plot of category frequencies, when  $x$  is a factor variable

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## Some simple plots:



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## 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()`
- ▶ Notice that objects in the global environment may mask objects in packages and attached data frames

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## Creating your own functions

A very simple example:

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

The function `logit` requires one argument  $p$  and produces the logit of  $p$ . Try `logit(0.5)`, or `logit(0.25)`, ...

More complex (but still simple):

```
simpsum <- function(x, dec=5) {
  m <- mean(x, na.rm=TRUE)
  s <- sd(x, na.rm=TRUE)
  round(c(mean=m, sd=s), dec) }
```

The function `simpsum` requires one argument `x`, but the second argument `dec` (no of decimal points in the output) has a default value 5. Try `simpsum(a)`, or `simpsum(a,dec=2)`.

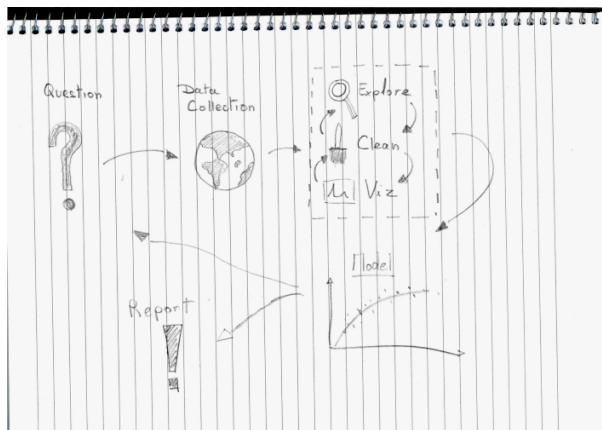
## Data manipulation with dplyr

Damien Georges

International Agency for Research on Cancer

August 2019 - Tartu

### Epidemiological study workflow



### Data manipulation tools



- ▶ R core function
- ▶ dplyr
- ▶ data.table
- ▶ ...

## Tidyverse (from [www.tidyverse.org](http://www.tidyverse.org))

### R packages for data science

The tidyverse is an opinionated collection of R packages designed for data science. All packages share an underlying design philosophy, grammar, and data structures.



pipe functions %>%

```
chill(fold(add(melt(add(chocolate, butter)),
                beat(add(eggs.white, cream))))
```

pipe functions %>%

```
chill(fold(add(melt(add(chocolate, butter)),
                beat(add(eggs.white, cream))))
```

```
chocolate %>%
  add(butter) %>%
  melt() %>%
  add(
    eggs.white %>%
      add(cream) %>%
      beat()
  ) %>%
  fold() %>%
  chill()
```

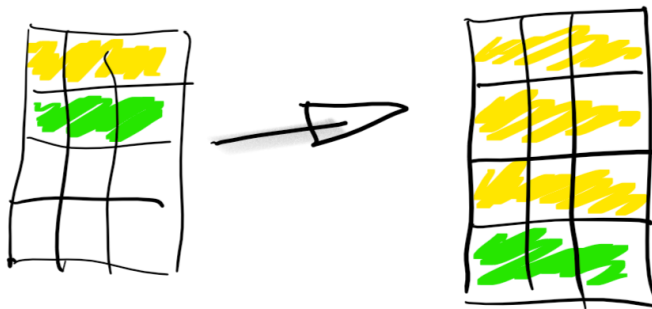
## code as you speak

Data manipulation with dplyr is done using a limited number of **verbs** corresponding to an action to be applied to a table.

- ▶ slice
- ▶ filter
- ▶ arrange
- ▶ select
- ▶ mutate
- ▶ group\_by
- ▶ summarize
- ▶ join
- ▶ ...

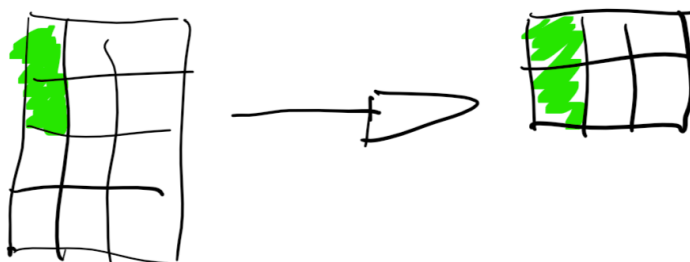
### select rows

```
dat %>% slice(c(1, 1, 1, 2))
```



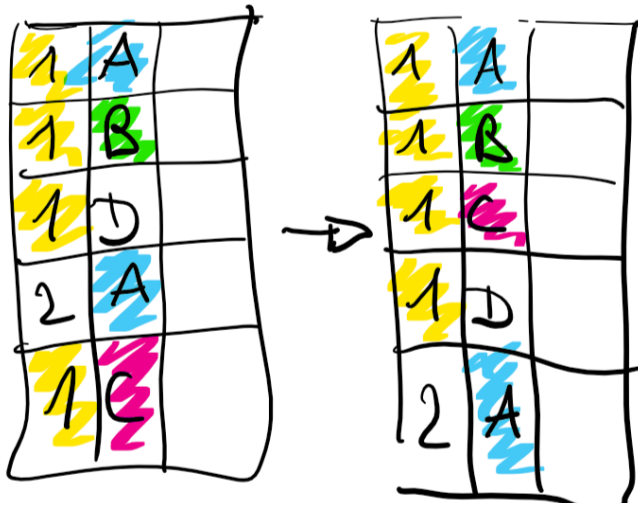
### select columns

```
dat %>% filter(C1 == 'green')
```



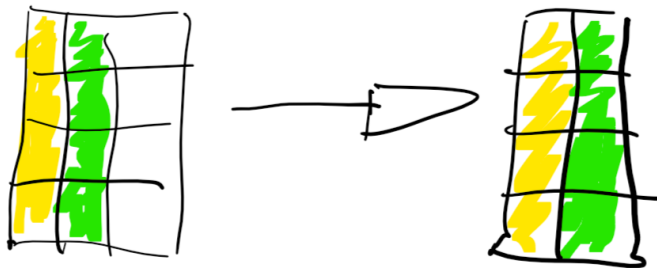
## arrange rows

```
dat %>% arrange(C1, C2)
```



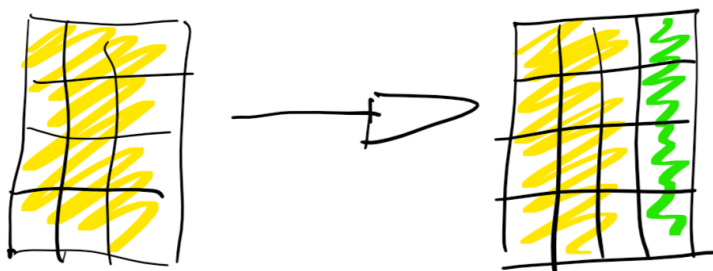
## columns selection

```
dat %>% select(C1, C2)
```



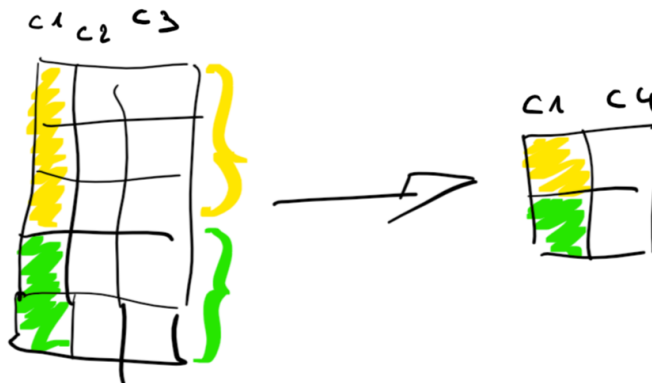
## create/modify columns

```
dat %>% mutate(C4 = C1 + C2 + C3)
```



## group and summarize data

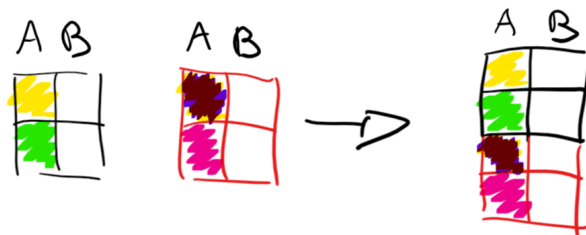
```
dat %>% group_by(C1) %>% summarize(C4 = mean(C2 + C3))
```



**note:** summarise() is an alias for summarize()

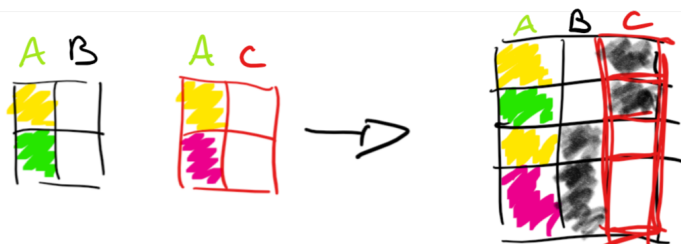
## bind and merge tables

```
dat1 %>% bind_rows(dat2)
```



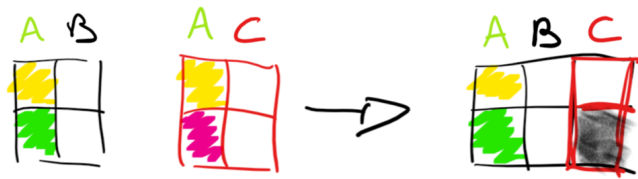
## bind and merge tables

```
dat1 %>% bind_rows(dat2)
```



## bind and merge tables

```
dat1 %>% left_join(dat2)
```



**note:** `right_join` will keep all rows of `dat2`

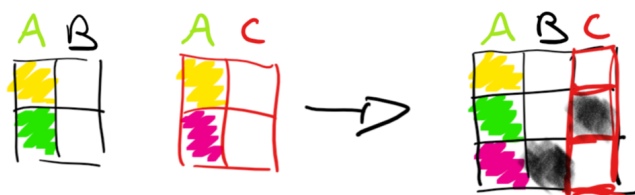
## bind and merge tables

```
dat1 %>% inner_join(dat2)
```



## bind and merge tables

```
dat1 %>% full_join(dat2)
```



# Poisson and Logistic Regression

Janne Pitkäniemi (initial slides EL)

Finnish Cancer Registry

Statistical Practice in Epidemiology (2019, Tartu)

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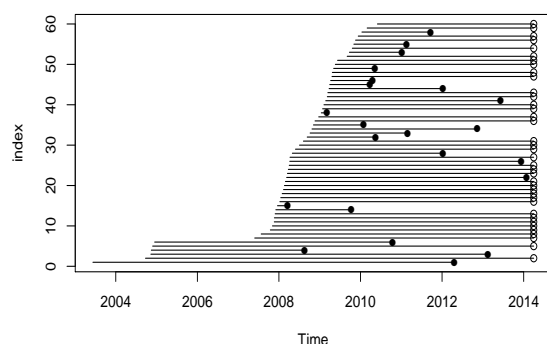
## Points to be covered

- ▶ Incidence rates, rate ratios and rate differences from *follow-up studies* can be computed by fitting *Poisson regression models*.
- ▶ Odds ratios can be computed from binary data by fitting *Logistic regression models*.
- ▶ Odds-ratios can be estimated from case-control studies.
- ▶ Both models are special instances of *Generalized linear models*.
- ▶ There are various ways to do these tasks in R.

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## The Estonian Biobank cohort: survival among the elderly

Follow-up of 60 random individuals aged 75-103 at recruitment, until death (●) or censoring (o) in April 2014 (linkage with the Estonian Causes of Death Registry).

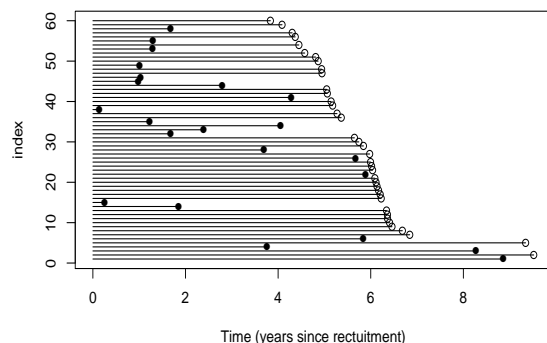


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## The Estonian Biobank cohort: survival among the elderly

Follow-up time for 60 random individuals aged 75-103 at recruitment (time-scale: time in study).



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## Events, dates and risk time

### ► Mortality as the outcome:

**d**: indicator for **status** at exit:

**1**: death observed

**0**: censored alive

### ► Dates:

doe = date of **E**ntry to follow-up,

dox = date of **eX**it, end of follow-up.

### ► Follow-up time (years) computed as:

$$y = (\text{dox} - \text{doe}) / 365.25$$

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## Crude overall rate computed by hand and model

Total no. cases, person-years & rate (/1000 y):

```
> D <- sum( d ); Y <- sum(y) ; R <- D/(Y/1000)
```

```
> round( c(D=D, Y=Y, R=R), 2)
```

```
   D      Y      R
884.00 11678.24  75.70
```

Two R-implementations of the rate estimation with Poisson regression:

A model with offset term

```
> m1 <- glm( D ~ 1,
             family=poisson, offset=log(Y))
```

```
> coef(m1)
```

```
( Intercept )
```

```
-2.581
```

A model with poisreg-family

```
> glm(cbind(D, Y) ~ 1,
      family=poisreg)
```

```
Coefficients :
```

```
( Intercept )
```

```
-2.581
```

*Why do we get the same results?*

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## Constant hazard — Poisson model

Let  $Y \sim \exp(\lambda)$ , then  $f(y; \lambda) = \lambda e^{-\lambda y} I(y > 0)$

Constant rate:  $\lambda(y) = \frac{f(y; \lambda)}{S(y; \lambda)} = \lambda$

Observed data  $\{(y_i, \delta_i); i = 1, \dots, n\}$ .

The likelihood  $L(\lambda) = \prod_{i=1}^n \lambda^{\delta_i} e^{-\lambda y_i}$  and

$$\log(L) = \sum_{i=1}^n [\delta_i \log(\lambda) - \lambda y_i]$$

Solving the *score equations*:  $\frac{\partial \log L(\lambda)}{\partial \lambda} = \sum \left[ \frac{\delta_i}{\lambda} - y_i \right]$   
 $= \frac{D}{\lambda} - Y = 0$  and  $D - \lambda Y = 0$

→ **maximum likelihood estimator** (MLE) of  $\lambda$ :

$$\hat{\lambda} = \frac{D}{Y} = \frac{\text{number of cases}}{\text{total person-time}} = \text{empirical rate!}$$

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## offset term — Poisson model

- ▶ Previous model without offset: Intercept 6.784=log(884)
- ▶ We should use an offset if we suspect that the underlying **population sizes (person-years) differ** for each of the observed counts – For example varying person-years by treatment group, sex, age,...
- ▶ We need a term in the model that "scales" the likelihood, but does not depend on model parameters (include a **term with reg. coef. fixed to 1**) – offset term is  $\log(y)$

$$\log\left(\frac{\mu}{y}\right) = \beta_0 + \beta_1 x_1$$
$$\log(\mu) = 1 \times \log(y) + \beta_0 + \beta_1 x_1$$

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## Comparing rates: The Thorotrast Study

- ▶ Cohort of seriously ill patients in Denmark on whom angiography of brain was performed.
- ▶ Exposure: contrast medium used in angiography,
  1. thor = thorotrast (with  $^{232}\text{Th}$ ), used 1935-50
  2. ctrl = other medium (?), used 1946-63
- ▶ Outcome of interest: death

doe = date of **E**ntry to follow-up,

dox = date of **eX**it, end of follow-up.

- ▶ `data(thoro)` in the `Epi` package.

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## Comparing rates: thorotrast vs. control

Tabulating cases, person-years & rates by group

```
> stat.table( contrast,
+             list( N = count(),
+                  D = sum(d),
+                  Y = sum(y),
+                  rate = ratio(d,y,1000) ) )
```

contrast	N	D	Y	rate
ctrl	1236	797.00	30517.56	26.12
thor	807	748.00	19243.85	38.87

Rate ratio,  $RR = 38.89/26.12 = 1.49$ ,  
 Std. error of log-RR,  $SE = \sqrt{1/748 + 1/797} = 0.051$ ,  
 Error factor,  $EF = \exp(1.96 \times 0.051) = 1.105$ ,  
 95% confidence interval for RR:  
 $(1.49/1.105, 1.49 \times 1.105) = (1.35, 1.64)$ .

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## Rate ratio estimation with Poisson regression

- Include contrast as the explanatory variable (factor).
- Insert person years in units that you want rates in

```
> m2 <- glm( d ~ contrast, offset=log(y/1000),
+            family = poisson )
> round( summary(m2)$coef, 4)[, 1:2]
```

	Estimate	Std. Error
( Intercept )	3.2626	0.0354
contrast thor	0.3977	0.0509

- Rate ratio and CI?  
Call function `ci.exp()` in `Epi`

```
> round( ci.exp( m2 ), 3 )
```

	exp(Est.)	2.5%	97.5%
(Intercept)	26.116	24.364	27.994
contrast thor	1.488	1.347	1.644

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## Rates in groups with Poisson regression

- Include contrast as the explanatory variable (factor).
- Remove the intercept (-1)
- Insert person-years in units that you want rates in

```
> m3 <- glm( d ~ contrast - 1,
+            offset=log(y/1000),
+            family = poisson )
> round( summary(m3)$coef, 4)[, 1:2]
```

	Estimate	Std. Error
contrast ctrl	3.2626	0.0354
contrast thor	3.6602	0.0366

```
> round( ci.exp( m3 ), 3 )
```

	exp(Est.)	2.5%	97.5%
contrast ctrl	26.116	24.364	27.994
contrast thor	38.870	36.181	41.757

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## Rates in groups with Poisson regression

- You can have it all in one go:

```
> CM <- rbind( c(1,0), c(0,1), c(-1,1) )
> rownames(CM) <- c("Ctrl","Thoro","Th vs.Ct")
> colnames(CM) <- names( coef(m3) )
> CM
```

	contrast	ctrl	contrast	thor
Ctrl		1		0
Thoro		0		1
Th vs. Ct		-1		1

```
> round( ci.exp( m3, ctr.mat=CM ),3 )
```

	exp(Est.)	2.5%	97.5%
Ctrl	26.116	24.364	27.994
Thoro	38.870	36.181	41.757
Th vs. Ct	1.488	1.347	1.644

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## Rate ratio estimation with Poisson regression

- Response may also be specified as individual *rates*:

d/y  
weights= instead of offset= are needed.

```
> m4<-glm( d/(y/1000)~contrast, weights=y/1000,
+          family=poisson)
> round( ci.exp(m4), 3 )
```

	exp(Est.)	2.5%	97.5%
(Intercept)	26.116	24.365	27.994
contrast thor	1.488	1.347	1.644

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## Rate difference estimation with Poisson regression

- The approach with d/y enables additive rate models too:

```
> m5 <-glm(d/(y/1000) ~contrast,weights=y/1000,
+          family=poisson(link="identity") )
> round( ci.exp(m5,Exp=F), 3 )
```

	Estimate	2.5%	97.5%
(Intercept)	26.116	24.303	27.929
contrast thor	12.753	9.430	16.077

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## Rates difference

- ▶ As before you can have it all:

```
> m6 <- glm( d/(y/1000) ~ contrast -1,
+ family = poisson(link="identity"),
+ weights = y/1000)
> round(ci.exp(m6, ctr.mat=CM, Exp=F ), 3)
```

```
      Estimate  2.5% 97.5%
Ctrl      26.116 24.303 27.929
Thoro     38.870 36.084 41.655
Th vs. Ct 12.753  9.430 16.077
```

```
> round( ci.exp( m3, ctr.mat=CM), 3 )
```

```
      exp(Est.)  2.5% 97.5%
Ctrl      26.116 24.364 27.994
Thoro     38.870 36.181 41.757
Th vs. Ct   1.488  1.347  1.644
```

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## Binary data: Treatment success Y/N

85 diabetes-patients with foot-wounds:

- ▶ Dalterapin (Dal)
- ▶ Placebo (Pl)

Treatment/Placebo given to diabetes patients, the design is prospective and outcome is measured better(Y)/worse(N). Is the probability of outcome more than 15% – yes, then use the risk difference or risk ratio (RR)

	Treatment group	
	Dalterapin	Placebo
Better	29	20
Worse	14	22
Total	43	42

$$\hat{p}_{\text{Dal}} = \frac{29}{43} = 67\% \quad \hat{p}_{\text{Pl}} = \frac{20}{42} = 47\%$$

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The difference between the probabilities is the fraction of the patients that benefit from the treatment:  $p_{\text{Dal}} - p_{\text{Pl}}$

```
> library(Epi)
> dlt <- rbind( c(29,14), c(20,22) )
> colnames( dlt ) <- c("Better","Worse")
> rownames( dlt ) <- c("Dal","Pl")
> kable(twoby2( dlt ), "latex")
```

2 by 2 table analysis :

	Better	Worse	P(Better)	95% conf. interval
Dal	29	14	0.6744	0.5226 0.7967
Pl	20	22	0.4762	0.3316 0.6249

	95% conf. interval
Relative Risk: 1.4163	0.9694 2.0692
Sample Odds Ratio: 2.2786	0.9456 5.4907
Conditional MLE Odds Ratio: 2.2560	0.8675 6.0405
Probability difference : 0.1982	-0.0110 0.3850

Exact P-value: 0.0808  
Asymptotic P-value: 0.0665

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## Logistic regression for binary data

For grouped binary data, the response is a two-column matrix with columns (successes,failures).

```
trt <- factor(c("Dal", "Pl"))
trt <- relevel( trt, 2 )
b1 <- glm( dlt ~ trt, family=binomial )
round( ci.exp( b1 ), 4 )
```

	exp(Est.)	2.5%	97.5%
( Intercept )	0.9091	0.4962	1.6657
trtDal	2.2786	0.9456	5.4907

- ▶ The default parameters in logistic regression are **odds** (the intercept:  $20/22 = 0.9090$ ) and the **odds-ratio** ( $((29/14)/(20/22)) = 2.28$ ).
- ▶ This is **NOT** what you want, because odds ratio is biased estimate of the risk ratio.(recall if  $p > 10\%$   $\frac{p}{1-p} \approx p$ )

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## Logistic regression for binary data - Risk ratio (Relative risk)

```
> library(Epi)
> library(xtable)
> dlt <- rbind( c(29,14), c(20,22) )
> diab<-expand.grid(dlt)
> colnames(diab)[1]<-"d"
> diab$out <- c("Better", "Better", "Worse", "Worse")
> diab$trt <- as.factor(c("Dal", "Pl", "Dal", "Pl"))
> diab$totals<-rep(rowSums(dlt),2)
> diab$trt<-relevel( diab$trt, 2 )
> print(xtable(diab,digits=c(0,0,0,0,0)),include.rownames = F)
```

d	out	trt	totals
29	Better	Dal	43
20	Better	Pl	42
14	Worse	Dal	43
22	Worse	Pl	42

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## Logistic regression for binary data - risk ratio

```
> library(Epi)
> library(xtable)
> b2 <- glm(d/totals~trt,
+           weights=totals,
+           family=binomial(link="log"),
+           data=diab[c(1,2),])
> xtable(round( ci.exp( b2 ), digits=6 ))
```

	exp(Est.)	2.5%	97.5%
(Intercept)	0.48	0.35	0.65
trtDal	1.42	0.97	2.07

Diabetics with Daltaparin treatment are 1.4 times likely to get better than those treated with placebo

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## Case-control study: Food-poisoning outbreak

- ▶ An outbreak of acute gastrointestinal illness (AGI) occurred in a psychiatric hospital in Dublin in 1996.
- ▶ Out of all 423 patients and staff members, 65 were affected during 27 to 31 August, 1996.
- ▶ 65 cases and 62 randomly selected control subjects were interviewed.
- ▶ Exposure of interest: chocolate mousse cake.
- ▶ 47 cases and 5 controls reported having eaten the cake.

Ref: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=188> – here original numbers somewhat modified.

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## Outbreak: crude summary of data

- ▶ Target population information
  - ▶  $N = 423$ , size of the whole study population
  - ▶  $D = 65$ , no. of cases of AGI
  - ▶  $B = 358$ , no. of non-cases
- ▶ Case-control data
  - ▶  $C = 62$ , no. of controls, random sample from 358 non-cases
  - ▶  $f = 62/358 = 0.173$ , sampling fraction of non-cases
  - ▶  $D1 = 47$  cases exposed to chocolate mousse
  - ▶  $D0 = 18$  unexposed cases
  - ▶  $C1 = 5$  controls exposed to chocolate mousse
  - ▶  $C0 = 57$  unexposed controls

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## Outbreak: results of analysis

Overall incidence proportion (IP) of AGI in the population

```
> D <- 65; N <- 423; IP <- D/N
> round(IP, 3)
[1] 0.154
```

Analysis of case-control data

```
> D1 <- 47; D0 <- D - D1;
> C <- 62; C1 <- 5; C0 <- C - C1
```

Case-control ratios by exposure (not as useful as the following!)

```
> round( c( D1/C1, D0/C0 ), 2)
[1] 9.40 0.32
```

Exposure odds in cases and controls

```
> round( c( D1/D0, C1/C0 ), 2)
[1] 2.61 0.09
```

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## Outbreak: results of analysis

Estimation of the incidence odds ratio (IOR) = exposure odds ratio

```
> IOR <- (D1/D0)/(C1/C0)
> SE.logIOR <- sqrt(1/D1 + 1/D0 + 1/C1 + 1/C0)
> CI.IOR <- IOR * exp( c(-1,1)*1.96*SE.logIOR )
> round( c(IOR, SE.logIOR, CI.IOR ), 2)
[1] 29.77 0.54 10.28 86.21
```

Same with glm model

```
> count<-c(D1,D0,C1,C0)
> cc<-c(1,1,0,0)
> exposed<-c(1,0,1,0)
> mousse<-data.frame(cbind(cc,exposed,count))
> ci.exp(glm(cc~exposed,weights=count,family="binomial",data=mousse))
               exp(Est.)      2.5%      97.5%
(Intercept)  0.3157895  0.1858913  0.5364586
exposed      29.7666667 10.2778305 86.2102603
```

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## Logistic regression in case-control studies

- Model for disease occurrence in the target population:

$$\ln \left[ \frac{p}{1-p} \right] = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

- Sampling fractions:  $P(\text{inclusion in study} \mid \text{control}) = s_{\text{ctr}}$   
 $P(\text{inclusion in study} \mid \text{case}) = s_{\text{cas}}$
- Model for observed case-control data:

$$\begin{aligned} \ln[\text{odds ( case } \mid \text{ incl.)}] &= \ln \left[ \frac{p}{1-p} \right] + \ln \left[ \frac{s_{\text{cas}}}{s_{\text{ctr}}} \right] \\ &= \left( \ln \left[ \frac{s_{\text{cas}}}{s_{\text{ctr}}} \right] + \beta_0 \right) + \beta_1 x_1 + \beta_2 x_2 \end{aligned}$$

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## Logistic regression in case-control studies

Analysis of  $P(\text{case} \mid \text{inclusion})$  — *i.e.* binary observations:

$$Y = \begin{cases} 1 & \sim \text{case} \\ 0 & \sim \text{control} \end{cases}$$

$$\ln[\text{odds ( case } \mid \text{ incl.)}] = \left( \ln \left[ \frac{s_{\text{cas}}}{s_{\text{ctr}}} \right] + \beta_0 \right) + \beta_1 x_1 + \beta_2 x_2$$

- Effect of covariates is estimated correctly.
- Intercept is meaningless  
depends on  $s_{\text{cas}}$  and  $s_{\text{ctr}}$  that are often unknown.

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## Conclusion: What did we learn?

- ▶ Poisson regression models.
- ▶ In Poisson models the response can be either:
  - ▶ case indicator  $d$  with `offset = log(y)`, or
  - ▶ rate  $d/y$  with `weights = y` or
  - ▶ case and person-years  $c(d,y)$  as response in glm with `poisreg-family` (Epi-package)
- ▶ Both may be fitted on either grouped data, or individual records.
- ▶ Binary outcome can be modeled with odds.
- ▶ Case-control studies:  
Odds-ratios can be computed by logistic regression models, but **Intercept** from model is **meaningless**.

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# Linear and generalized linear models

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Statistical Practice in Epidemiology with **R**  
23 to 28 August, 2019  
University of Tartu, Estonia

## Outline

- ▶ Simple linear regression.
- ▶ Fitting a model and extracting results.
- ▶ Predictions and diagnostics.
- ▶ Categorical factors and contrast matrices.
- ▶ Main effects and interactions.
- ▶ Generalized linear models.
- ▶ Modelling curved effects.

Linear and generalized linear models

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## Variables in generalized linear models

- ▶ The **outcome** or **response** variable must be numeric.
- ▶ Main types of response variables are
  - Metric or continuous (a measurement with units)
  - Binary (two values coded 0/1)
  - Failure (does the subject fail at end of follow-up)
  - Count (aggregated failure data, number of cases)
- ▶ **Explanatory** variables or **regressors** can be
  - Numeric or quantitative variables
  - Categorical factors, represented by class indicators or contrast matrices.

Linear and generalized linear models

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## The births data in Epi

id: Identity number for mother and baby.  
bweight: Birth weight of baby.  
lowbw: Indicator for birth weight less than 2500 g.  
gestwks: Gestation period in weeks.  
preterm: Indicator for gestation period less than 37 weeks.  
matage: Maternal age.  
hyp: Indicator for maternal hypertension (0 = no, 1 = yes).  
sex: Sex of baby (1 = male, 2 = female).

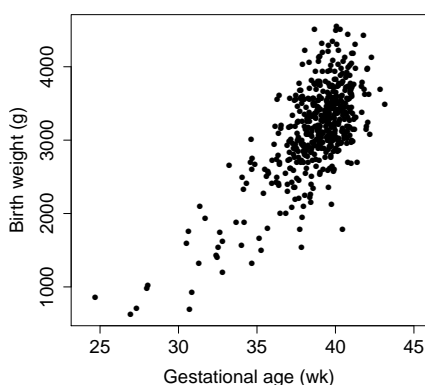
Declaring and transforming some variables as factors:

```
> library(Epi) ; data(births)
> births <- transform(births,
+   hyp = factor(hyp, labels=c("N", "H")),
+   sex = factor(sex, labels=c("M", "F")),
+   gest4 = cut(gestwks,breaks=c(20, 35, 37, 39, 45), right=FALSE) )
> births <- subset(births, !is.na(gestwks))
```

Linear and generalized linear models

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## Birth weight and gestational age



```
> with(births, plot(bweight ~ gestwks, xlim = c(24,45), pch = 16, cex.axis=1.5, cex.lab = 1.5,
+   xlab= "Gestational age (wk)", ylab= "Birth weight (g)" ) )
```

Linear and generalized linear models

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## Metric response, numeric explanatory variable

Roughly linear relationship btw bweight and gestwks

→ Simple **linear regression model** fitted.

```
> m <- lm(bweight ~ gestwks, data=births)
```

- ▶ `lm()` is the function that fits linear regression models, assuming **Gaussian** distribution for **error** terms.
- ▶ `bweight ~ gestwks` is the **model formula**
- ▶ `m` is a **model object** belonging to class "lm".

```
> coef(m) – Printing the estimated regression coefficients
```

(Intercept)	gestwks
-4489.1	197.0

Interpretation of **intercept** and **slope**?

Linear and generalized linear models

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## Model object and extractor functions

Model object = **list** of different elements, each being separately accessible. – See `str(m)` for the full list.

Functions that extract results from the fitted model object

- ▶ `summary(m)` – lots of output
- ▶ `coef(m)` – beta-hats only (see above)
- ▶ `ci.lin(m)[,c(1,5,6)]` –  $\hat{\beta}_j$ s plus confidence limits

	Estimate	2.5%	97.5%
(Intercept)	-4489.1	-5157.3	-3821.0
gestwks	197.0	179.7	214.2

This function is in Epi package

- ▶ `anova(m)` – Analysis of Variance Table

Linear and generalized linear models

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## Other extractor functions, for example

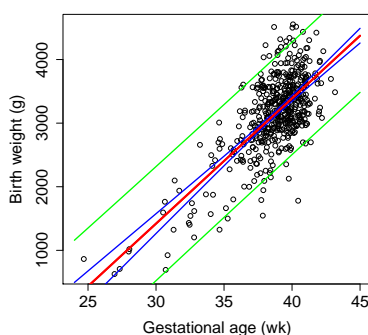
- ▶ `fitted(m)`, `resid(m)`, `vcov(m)`, ...
- ▶ `predict(m, newdata = ..., interval=...)`
  - Predicted responses for desired combinations of new values of the regressors – `newdata`
  - Argument `interval` specifies whether **confidence** intervals for the *mean* response or **prediction** intervals for *individual* responses are returned.
- ▶ `plot(m)` – produces various diagnostic plots based on residuals (raw or standardized)

Many of these are special **methods** for certain **generic functions**, aimed at acting on objects of class “lm”.

Linear and generalized linear models

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## Fitted values, confidence & prediction intervals

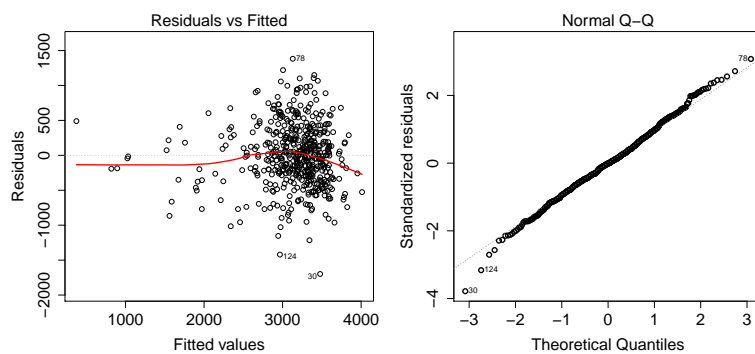


```
> nd <- data.frame( gestwks = seq(24, 45, by = 0.25) )
> pr.c1 <- predict( m, newdata=nd, interval="conf" )
> pr.p1 <- predict( m, newdata=nd, interval="pred" )
> with(births, plot(bweight ~ gestwks, xlim = c(24,45), cex.axis=1.5, cex.lab = 1.5, xlab = 'Gestation' )
> matlines( nd$gestwks, pr.c1, lty=1, lwd=c(3,2,2), col=c('red','blue','blue'))
> matlines( nd$gestwks, pr.p1, lty=1, lwd=c(3,2,2), col=c('red','green','green'))
```

Linear and generalized linear models

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## A couple of diagnostic plots



```
> par(mfrow=c(1,2))
> plot(m, 1:2, cex.lab = 1.5, cex.axis=1.5, cex.caption=1.5, lwd=2)
```

- Some deviation from linearity?
- Reasonable agreement with Gaussian error assumption?

Linear and generalized linear models

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## Factor as an explanatory variable

- How bweight depends on maternal hypertension?

```
> mh <- lm( bweight ~ hyp, data=births)
```

	Estimate	2.5%	97.5%
(Intercept)	3198.9	3140.2	3257.6
hypH	-430.7	-585.4	-275.9

- Removal of intercept → mean bweights by hyp:

```
> mh2 <- lm( bweight ~ -1 + hyp, data = births)
> coef(mh2)
      hypN      hypH
3198.9 2768.2
```

- Interpretation:  $-430.7 = 2768.2 - 3198.9$  = difference between level 2 vs. reference level 1 of hyp

Linear and generalized linear models

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## Additive model with both gestwks and hyp

- Joint effect of hyp and gestwks under additivity is modelled e.g. by updating a simpler model:

```
> mhg <- update(mh, . ~ . + gestwks)
```

	Estimate	2.5%	97.5%
(Intercept)	-4285.0	-4969.7	-3600.3
hypH	-143.7	-259.0	-28.4
gestwks	192.2	174.7	209.8

- The effect of hyp: H vs. N is attenuated (from  $-430.7$  to  $-143.7$ ).
- This suggests that much of the effect of hypertension on birth weight is mediated through a shorter gestation period among hypertensive mothers.

Linear and generalized linear models

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## Model with interaction of hyp and gestwks

- ▶ `mhgi <- lm(bweight ~ hyp + gestwks + hyp:gestwks, data = births)`
- ▶ Or with shorter formula: `bweight ~ hyp * gestwks`

	Estimate	2.5%	97.5%
(Intercept)	-3960.8	-4758.0	-3163.6
hypH	-1332.7	-2841.0	175.7
gestwks	183.9	163.5	204.4
hypH:gestwks	31.4	-8.3	71.1
- ▶ Estimated slope: 183.9 g/wk in reference group N and  $183.9 + 31.4 = 215.3$  g/wk in hypertensive mothers.
- ⇔ For each additional week the difference in mean bweight between H and N group increases by 31.4 g.
- ▶ *Interpretation of Intercept and “main effect” hypH?*

Linear and generalized linear models

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## Model with interaction (cont'd)

More interpretable parametrization obtained if `gestwks` is **centered** at some reference value, using e.g. the **insulate** operator `I()` for explicit transformation of an original term.

- ▶ `mi2 <- lm(bweight ~ hyp*I(gestwks-40), ...)`

	Estimate	2.5%	97.5%
(Intercept)	3395.6	3347.5	3443.7
hypH	-77.3	-219.8	65.3
I(gestwks - 40)	183.9	163.5	204.4
hypH:I(gestwks - 40)	31.4	-8.3	71.1
- ▶ Main effect of `hyp` =  $-77.3$  is the difference between H and N at `gestwks` = 40.
- ▶ Intercept = 3395.6 is the estimated mean bweight at the reference value 40 of `gestwks` in group N.

Linear and generalized linear models

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## Factors and contrasts in R

- ▶ A categorical explanatory variable or **factor** with  $L$  levels will be represented by  $L - 1$  linearly independent columns in the **model matrix** of a linear model.
- ▶ These columns can be defined in various ways implying alternative **parametrizations** for the effect of the factor.
- ▶ Parametrization is defined by given type of **contrasts**.
- ▶ Default: **treatment** contrasts, in which 1st class is the **reference**, and regression coefficient  $\beta_k$  for class  $k$  is interpreted as  $\beta_k = \mu_k - \mu_1$
- ▶ Own parametrization may be tailored by function `C()`, with the pertinent **contrast matrix** as argument.
- ▶ Or, use `ci.lin(mod, ctr.mat = CM)` after fitting.

Linear and generalized linear models

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## Two factors: additive effects

- ▶ Factor  $X$  has 3 levels,  $Z$  has 2 levels – Model:

$$\mu = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \gamma_1 Z_1 + \gamma_2 Z_2$$

- ▶  $X_1$  (reference),  $X_2, X_3$  are the indicators for  $X$ ,
- ▶  $Z_1$  (reference),  $Z_2$  are the indicators for  $Z$ .
- ▶ Omitting  $X_1$  and  $Z_1$  the model for mean is:

$$\mu = \alpha + \beta_2 X_2 + \beta_3 X_3 + \gamma_2 Z_2$$

with predicted means  $\mu_{jk}$  ( $j = 1, 2, 3; k = 1, 2$ ):

		$Z = 1$	$Z = 2$
$X$	1	$\mu_{11} = \alpha$	$\mu_{11} = \alpha + \gamma_2$
	2	$\mu_{21} = \alpha + \beta_2$	$\mu_{22} = \alpha + \beta_2 + \gamma_2$
	3	$\mu_{31} = \alpha + \beta_3$	$\mu_{32} = \alpha + \beta_3 + \gamma_2$

Linear and generalized linear models

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## Two factors with interaction

- ▶ Effect of  $Z$  differs at different levels of  $X$ :

		$Z = 1$	$Z = 2$
$X$	1	$\mu_{11} = \alpha$	$\mu_{12} = \alpha + \gamma_2$
	2	$\mu_{21} = \alpha + \beta_2$	$\mu_{22} = \alpha + \beta_2 + \gamma_2 + \delta_{22}$
	3	$\mu_{31} = \alpha + \beta_3$	$\mu_{32} = \alpha + \beta_3 + \gamma_2 + \delta_{32}$

- ▶ How much the effect of  $Z$  (level 2 vs. 1) changes when the level of  $X$  is changed from 1 to 3:

$$\begin{aligned}\delta_{32} &= (\mu_{32} - \mu_{31}) - (\mu_{12} - \mu_{11}) \\ &= (\mu_{32} - \mu_{12}) - (\mu_{31} - \mu_{11}),\end{aligned}$$

= how much the effect of  $X$  (level 3 vs. 1) changes when the level of  $Z$  is changed from 1 to 2.

- ▶ See the exercise: interaction of hyp and gest4.

Linear and generalized linear models

16/ 22

## Contrasts in R

- ▶ All contrasts can be implemented by supplying a suitable **contrast function** giving the **contrast matrix** e.g:

```
> contr.cum(3)      > contr.sum(3)
1 0 0                1  1  0
2 1 0                2  0  1
3 1 1                3 -1 -1
```

- ▶ In model formula factor name faktori can be replaced by expression like `C(faktori, contr.cum)`.
- ▶ Function `ci.lin()` has an option for calculating CI's for linear functions of the parameters of a fitted model `mall` when supplied by a relevant contrast matrix
 

```
> ci.lin(mall, ctr.mat = CM)[ , c(1,5,6)]
```

 → No need to specify contrasts in model formula!

Linear and generalized linear models

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## From linear to generalized linear models

- ▶ An alternative way of fitting our 1st Gaussian model:  

```
> m <- glm(bweight ~ gestwks, family=gaussian, data=births)
```
- ▶ Function `glm()` fits **generalized linear models** (GLM).
- ▶ Requires specification of the
  - **family** – i.e. the assumed “error” distribution for  $Y_i$ s,
  - **link** function – a transformation of the expected  $Y_i$ .
- ▶ Covers common models for other types of response variables and distributions, too, e.g. **logistic** regression for binary responses and **Poisson** regression for counts.
- ▶ Fitting: method of **maximum likelihood**.
- ▶ Many extractor functions for a `glm` object similar to those for an `lm` object.

Linear and generalized linear models

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## More about numeric regressors

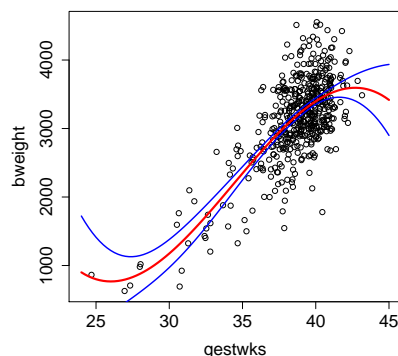
What if dependence of  $Y$  on  $X$  is non-linear?

- ▶ **Categorize** the values of  $X$  into a factor.
  - Continuous effects violently discretized by often arbitrary cutpoints. – Inefficient.
- ▶ Fit a low-degree (e.g. 2 to 4) **polynomial** of  $X$ .
  - Tail behaviour may be problematic.
- ▶ Use **fractional polynomials**.
  - Invariance problems. Only useful if  $X = 0$  is well-defined.
- ▶ Use a **spline** model: smooth function  $s(X; \beta)$ . – See Martyn’s lecture
  - More flexible models that act locally.
  - Effect of  $X$  reported by graphing  $\hat{s}(X; \beta)$  & its CI

Linear and generalized linear models

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## Mean bweight as 3rd order polynomial of gestwks



```
> mp3 <- update( m, . ~ . - gestwks + poly(gestwks, 3) )
```

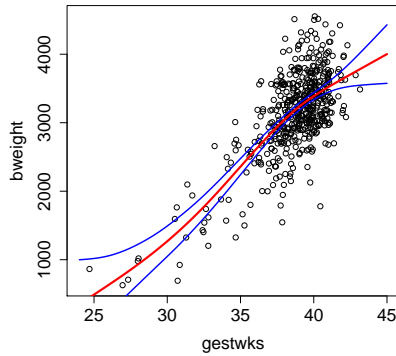
- ▶ The model is linear in parameters with 4 terms & 4 df.
- ▶ Otherwise good, but the tails do not behave well.

Linear and generalized linear models

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## Penalized spline model with cross-validation



```
> library(mgcv)
> mpen <- gam( bweight ~ s(gestwks), data = births)
```

- ▶ Looks quite nice.
- ▶ Model  $df \approx 4.2$ ; close to 4, as in the 3rd degree polynomial model.

Linear and generalized linear models

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## What was covered

- ▶ A wide range of models from simple linear regression to splines.
- ▶ R functions fitting linear and generalized models:  
lm() and glm().
- ▶ Parametrization of categorical explanatory factors; contrast matrices.
- ▶ Extracting results and predictions:  
ci.lm(), fitted(), predict(), ...
- ▶ Model diagnostics:  
resid(), plot.lm(), ...

Linear and generalized linear models

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# Everything You Ever Wanted to Know about Splines...

Martyn Plummer

University of Warwick

August 2019

Categorization and its discontents 00000  
 Join the dots 00000000000  
 Brownian motion 00000000000  
 Smoothing splines 0000  
 Conclusions 00000000

## Overview

## Categorization and its discontents

## Join the dots

## Brownian motion

## Smoothing splines

## Conclusions

Categorization and its discontents
Join the dots
Brownian motion
Smoothing splines
Conclusions

## Introduction

- Splines are a flexible class of models that can be helpful for representing dose-response relationships in epidemiology
- In this course we will be using spline models extensively.
- However, spline models are widely misunderstood.
- The purpose of this lecture is to give a conceptual background on where spline models come from.

## Outline

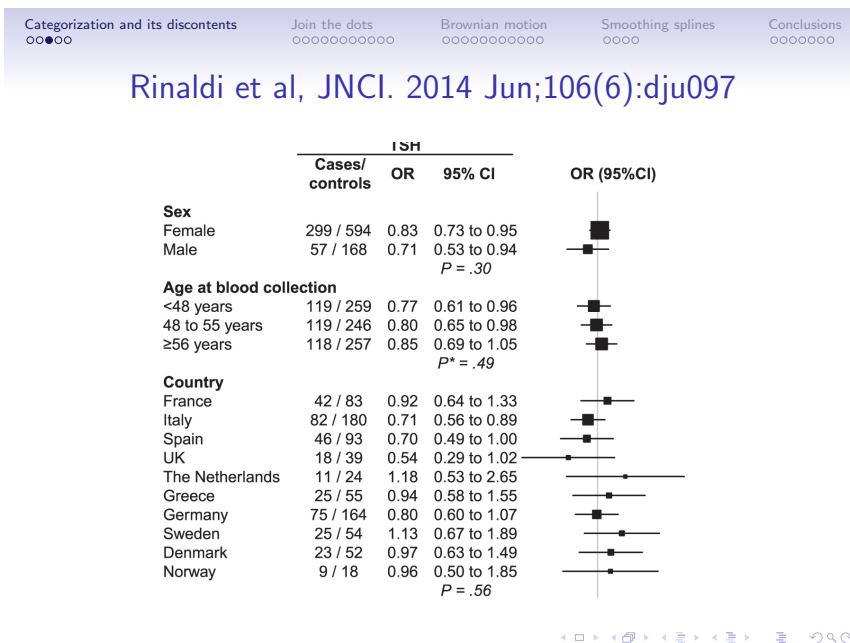
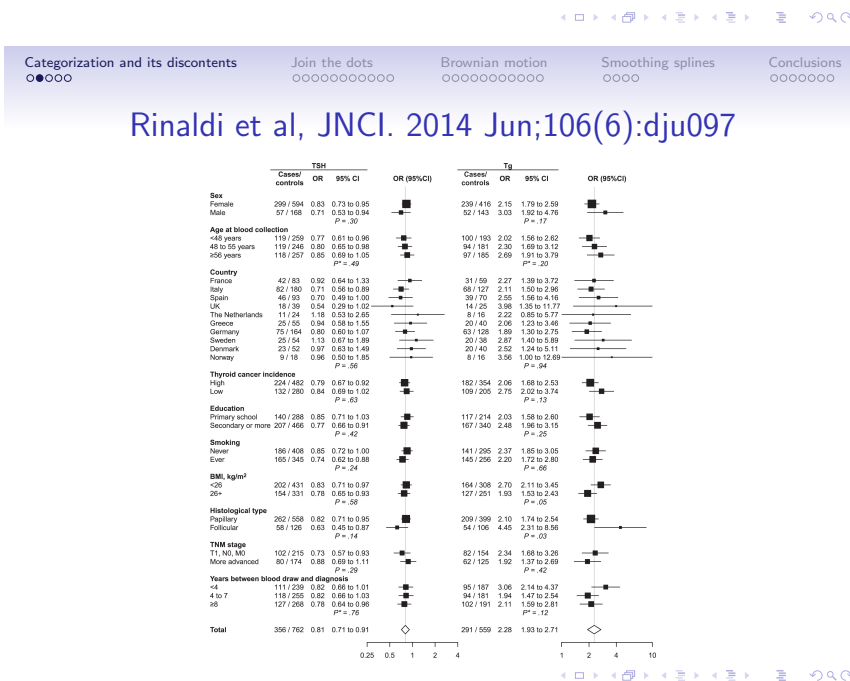
Categorization and its discontents

Join the dots

Brownian motion

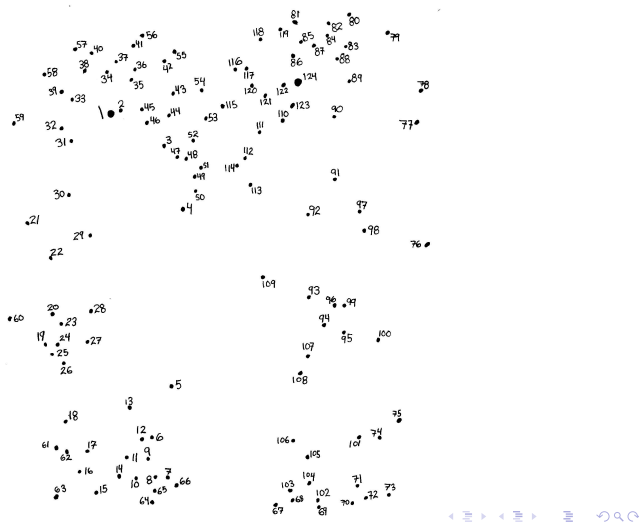
Smoothing splines

Conclusions

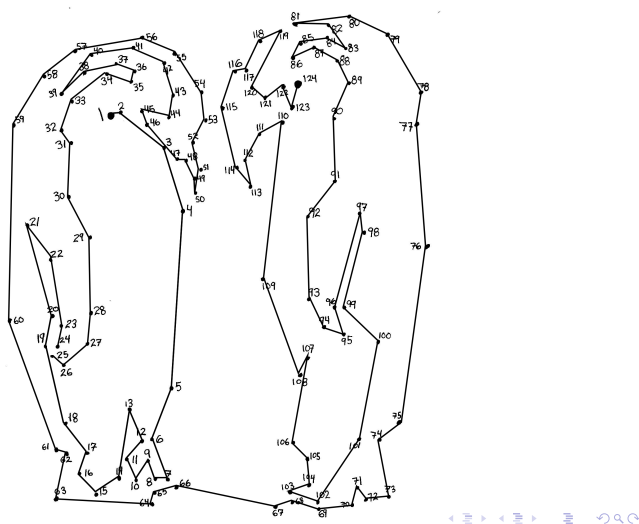




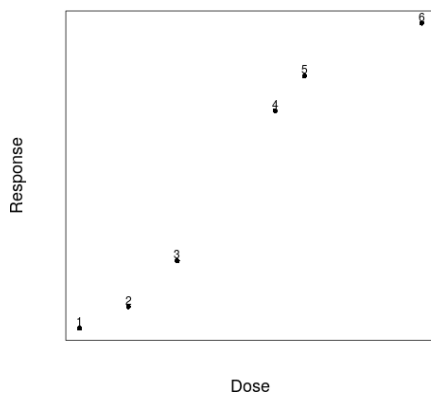
## Join the dots



## Join the dots



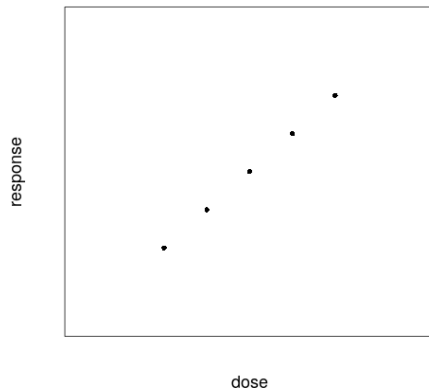
## Linear interpolation



- Suppose a dose response curve is known exactly at certain points
- We can fill in the gaps (interpolate) by drawing a straight (linear) line between adjacent points

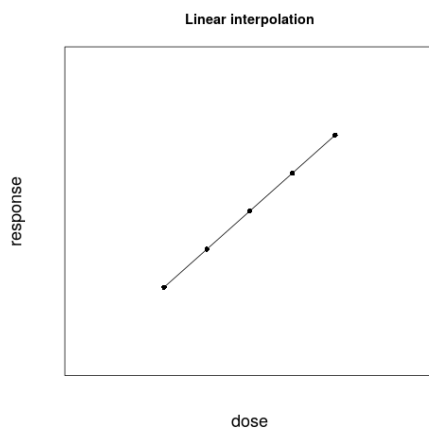


## Extrapolation



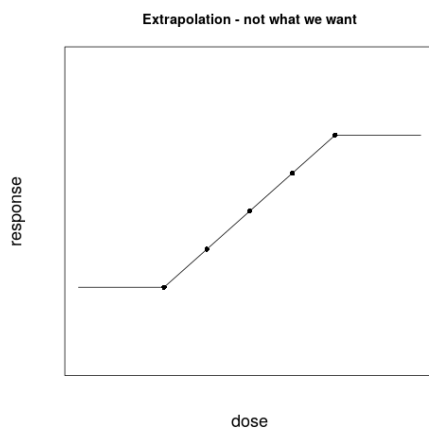
- Linear interpolation fits a linear dose-response curve exactly
- But it breaks down when we try to extrapolate

## Extrapolation



- Linear interpolation fits a linear dose-response curve exactly
- But it breaks down when we try to extrapolate

## Extrapolation



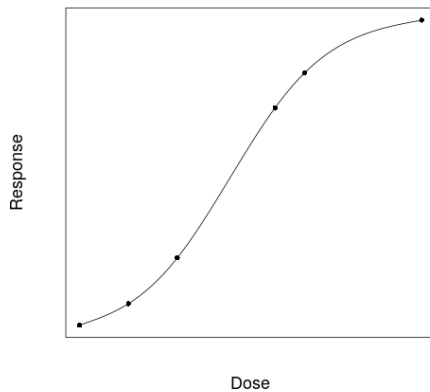
- Linear interpolation fits a linear dose-response curve exactly
- But it breaks down when we try to extrapolate







## An interpolating cubic spline



- The smoothest curve that goes through the observed points is a cubic spline.

Navigation icons: back, forward, search, etc.

## Properties of cubic splines

- A cubic spline consists of a sequence of curves of the form

$$f(x) = a + bx + cx^2 + dx^3$$

for some coefficients  $a, b, c, d$ , in between each observed point.

- The cubic curves are joined at the observed points (knots)
- The cubic curves match where they meet at the knots
  - Same value  $f(x)$
  - Same slope  $\partial f / \partial x$
  - Same curvature  $\partial^2 f / \partial x^2$

Navigation icons: back, forward, search, etc.

## Outline

Categorization and its discontents

Join the dots

Brownian motion

Smoothing splines

Conclusions

Navigation icons: back, forward, search, etc.











## Fitting a smoothing spline

Minimize

$$\sum_i (y_i - f(x_i))^2 + \lambda \int \left( \frac{\partial^2 f}{\partial x^2} \right)^2 dx$$

Or, more generally

$$\text{Deviance} + \lambda * \text{Roughness penalty}$$

Size of tuning parameter  $\lambda$  determines compromise between model fit (small  $\lambda$ ) and smoothness (large  $\lambda$ ).

## How to choose the tuning parameter $\lambda$

This is a statistical problem. There are various statistical approaches:

- Restricted maximum likelihood (REML)
- Cross-validation
- Bayesian approach (with prior on smoothness)

At least the first two should be available in most software.

## Outline

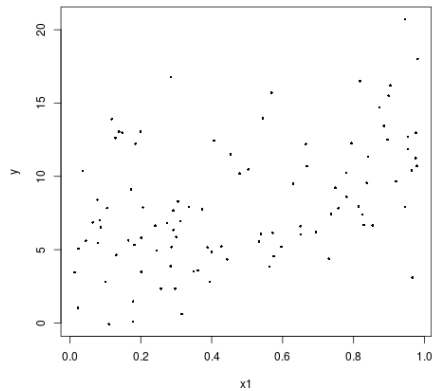
## Conclusions





## Penalized spline

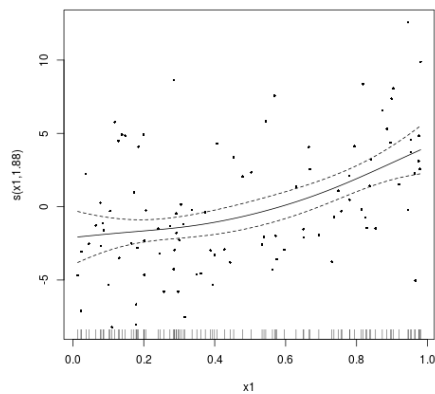
### Some simulated data



- A gam fit to some simulated data
- Model has 9 degrees of freedom
- Smoothing reduces this to 2.88 effective degrees of freedom

## Penalized spline

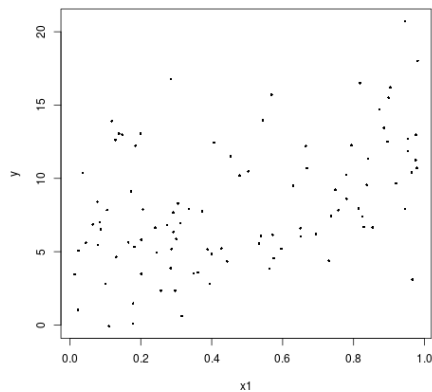
### A gam fit with default options



- A gam fit to some simulated data
- Model has 9 degrees of freedom
- Smoothing reduces this to 2.88 effective degrees of freedom

## Unpenalized spline

### Some simulated data



- An unpenalized spline using the same spline basis as the gam fit.
- Model has 9 degrees of freedom



## More Advanced Graphics in R

Martyn Plummer

University of Warwick, UK

SPE 2019, Tartu

Overview of graphics systems ○○○○○○○	Device handling ○○○	Base graphics ○○○○○○○○○	Lattice graphics ○○○○○○○	Grid graphics ○○○
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### Outline

Overview of graphics systems

Device handling

Base graphics

Lattice graphics

Grid graphics

Overview of graphics systems ●○○○○○	Device handling ○○○	Base graphics ○○○○○○○○○	Lattice graphics ○○○○○○○	Grid graphics ○○○
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### Graphics Systems in R

R has several different graphics systems:

- ▶ Base graphics (the `graphics` package)
- ▶ Lattice graphics (the `lattice` package)
- ▶ Grid graphics (the `grid` package)
- ▶ Grammar of graphics (the `ggplot2` package)

Why so many? Which one to use?

## Base Graphics

- ▶ The oldest graphics system in R.
- ▶ Based on S graphics (Becker, Chambers and Wilks, *The New S Language*, 1988)
- ▶ Implemented in the base package `graphics`
  - ▶ Loaded automatically so always available
- ▶ Ink on paper model; once something is drawn “the ink is dry” and it cannot be erased or modified.

## Lattice Graphics

- ▶ A high-level data visualization system with an emphasis on multivariate data
- ▶ An implementation of Trellis graphics, first described by William Cleveland in the book *Visualizing Data*, 1993.
- ▶ Implemented in the base package `lattice`.
- ▶ More fully described by the `lattice` package author Deepayan Sarkar in the book *Lattice: Multivariate Data Visualization with R*, 2008.

## Grammar of Graphics

- ▶ Originally described by Leland Wilkinson in the book *The Grammar of Graphics*, 1999 and implemented in the statistical software nVizn (part of SPSS)
- ▶ Statistical graphics, like natural languages, can be broken down into components that must be combined according to certain rules.
- ▶ Provides a *pattern language* for graphics:
  - ▶ geometries, statistics, scales, coordinate systems, aesthetics, themes, ...
- ▶ Implemented in R in the CRAN package `ggplot2`
- ▶ Described more fully by the `ggplot2` package author Hadley Wickham in the book *ggplot2: Elegant Graphics for Data Analysis*, 2009.

## Grid Graphics

- ▶ A complete rewrite of the graphics system of R, independent of base graphics.
- ▶ Programming with graphics:
  - ▶ Grid graphics commands create graphical objects (Grobs)
  - ▶ Printing a Grob displays it on a graphics device
  - ▶ Functions can act on grobs to modify or combine them
- ▶ Implemented in the base package `grid`, and extended by CRAN packages `gridExtra`, `gridDebug`, ...
- ▶ Described by the package author Paul Murrell in the book *R Graphics (2nd edition)*, 2011.

## Putting It All Together

- ▶ Base graphics are the default, and are used almost exclusively in this course
- ▶ `lattice` and `ggplot2` are alternate, high-level graphics packages
- ▶ `grid` provides alternate low-level graphics functions.
  - ▶ A *domain-specific language* for graphics within R
  - ▶ Underlies both `lattice` and `ggplot`
  - ▶ Experts only
- ▶ All graphics packages take time to learn...

## Graphics Devices

Graphics devices are used by all graphics systems (base, lattice, ggplot2, grid).

- ▶ Plotting commands will draw on the current *graphics device*
- ▶ This default graphics device is a window on your screen:
  - On Windows `windows()`
  - On Unix/Linux `x11()`
  - On Mac OS X `quartz()`It normally opens up automatically when you need it.
- ▶ You can have several graphics devices open at the same time (but only one is current)

## Graphics Device in RStudio

RStudio has its own graphics device `RStudioGD` built into the graphical user interface

- ▶ You can see the contents in a temporary, larger window by clicking the zoom button.
- ▶ You can write the contents directly to a file with the export menu
- ▶ Sometimes small size of the `RStudioGD` causes problems. Open up a new device calling `RStudioGD()`. This will appear in its own window, free from the GUI.

Navigation icons: back, forward, search, etc. 10/30

## Writing Graphs to Files

There are also non-interactive graphics devices that write to a file instead of the screen.

`pdf` produces Portable Document Format files

`win.metafile` produces Windows metafiles that can be included in Microsoft Office documents (windows only)

`postscript` produces postscript files

`png`, `bmp`, `jpeg` all produce bitmap graphics files

- ▶ Turn off a graphics device with `dev.off()`. Particularly important for non-interactive devices.
- ▶ Plots may look different in different devices

Navigation icons: back, forward, search, etc. 11/30

## Types of Plotting Functions

- ▶ High level
  - ▶ Create a new page of plots with reasonable default appearance.
- ▶ Low level
  - ▶ Draw elements of a plot on an existing page:
    - ▶ Draw title, subtitle, axes, legend ...
    - ▶ Add points, lines, text, math expressions ...
- ▶ Interactive
  - ▶ Querying mouse position (`locator`), highlighting points (`identify`)

Navigation icons: back, forward, search, etc. 12/30

## Basic x-y Plots

- ▶ The `plot` function with one or two numeric arguments
- ▶ Scatterplot or line plot (or both) depending on `type` argument: "l" for lines, "p" for points (the default), "b" for both, plus quite a few more
- ▶ Also: formula interface, `plot(y~x)`, with arguments similar to the modeling functions like `lm`

## Customizing Plots

- ▶ Most plotting functions take optional parameters to change the appearance of the plot
  - ▶ e.g., `xlab`, `ylab` to add informative axis labels
- ▶ Most of these parameters can be supplied to the `par()` function, which changes the default behaviour of subsequent plotting functions
- ▶ Look them up via `help(par)`! Here are some of the more commonly used:
  - ▶ Point and line characteristics: `pch`, `col`, `lty`, `lwd`
  - ▶ Multiframe layout: `mfrow`, `mfcol`
  - ▶ Axes: `xlim`, `ylim`, `xaxt`, `yaxt`, `log`

## Adding to Plots

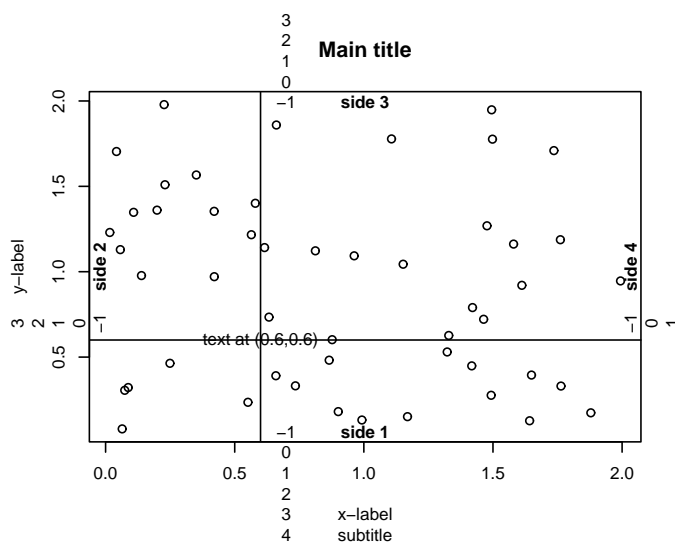
- ▶ `title()` add a title above the plot
- ▶ `points()`, `lines()` adds points and (poly-)lines
- ▶ `text()` text strings at given coordinates
- ▶ `abline()` line given by coefficients ( $a$  and  $b$ ) or by fitted linear model
- ▶ `axis()` adds an axis to one edge of the plot region. Allows some options not otherwise available.





## Demo 2

```
x <- runif(50,0,2)
y <- runif(50,0,2)
plot(x, y, main="Main title", sub="subtitle",
      xlab="x-label", ylab="y-label")
text(0.6,0.6,"text at (0.6,0.6)")
abline(h=.6,v=.6)
for (side in 1:4)
  mtext(-1:4,side=side,at=.7,line=-1:4)
mtext(paste("side",1:4), side=1:4, line=-1,font=2)
```



The `lattice` package provides functions that produce similar plots to base graphics (with a different “look and feel”)

base	lattice
plot	xyplot
hist	histogram
boxplot	bwplot
barplot	barchart
heatmap, contour	levelplot
dotchart	dotplot

Lattice graphics can also be used to explore *multi-dimensional data*





## A Few Words on Grid Graphics

- ▶ Experts only, but ...
- ▶ Recall that `lattice` and `ggplot2` both use `grid`
- ▶ The key concepts you need are *grobs* and *viewports*

## Grobs: Graphical Objects

- ▶ Grobs are created by plotting functions in `grid`, `lattice`, `ggplot2`
- ▶ Grobs are only displayed when they are printed
- ▶ Grobs can be modified or combined before being displayed
- ▶ The `ggplot2` package uses the `+` operator to combine grobs representing different elements of the plot

## Viewports

- ▶ The plotting region is divided into viewports
- ▶ Grobs are displayed inside a viewport
- ▶ The panels in lattice graphics are examples of viewports, but in general
  - ▶ Viewports can be different sizes (inches, centimetres, lines of text, or relative units)
  - ▶ Each viewport may have its own coordinate systems

# Survival analysis with competing risks

Janne Pitkäniemi (initial slides EL)

Finnish Cancer Registry

Statistical Practice in Epidemiology (2019, Tartu)

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## Points to be covered

1. Survival or time to event data & censoring.
2. Competing risks: event-specific cumulative incidences & hazards.
3. Kaplan–Meier and Aalen–Johansen estimators.
4. Regression modelling of hazards: Cox model.
5. Packages `survival`, `mstate`, `cmprisk`.
6. Functions `Surv()`, `survfit()`, `plot.survfit()`, `coxph()`.

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## Survival time – time to event

**Time** spent (`lex.dur`) in a given **state** (`lex.Cst`) from its beginning till a certain *endpoint* or *outcome event* (`lex.Xst`) or *transition* occurs, changing the state to another.

Examples of such times and outcome events:

- ▶ lifetime: birth → death,
- ▶ duration of marriage: wedding → divorce,
- ▶ healthy exposure time:  
start of exposure → onset of disease,
- ▶ clinical survival time:  
diagnosis of a disease → death.

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## Ex. Survival of 338 oral cancer patients

Important variables:

- ▶ **time** = duration of patientship from diagnosis (**entry**) till death (**death**) or censoring (**Alive**), (`lex.Cst is (Alive)`)
- ▶ **event** = indicator for the outcome and its observation at the end of follow-up (**exit**):  
0 = censoring,  
1 = death from oral cancer

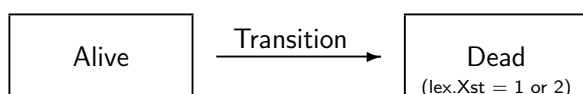
Special features:

- ▶ Two possible endpoints
- ▶ Censoring – incomplete observation of the survival time.

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## Set-up of classical survival analysis

- ▶ **Two-state model**: only one type of event changes the initial state.
- ▶ Major applications: analysis of lifetimes since birth and of survival times since diagnosis of a disease until death from any cause.



- ▶ **Censoring**: Death and final lifetime not observed for some subjects due to emigration or closing the follow-up while they are still alive

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## Distribution concepts: hazard function

The **hazard rate** or **intensity** function  $\lambda(t)$

$$\lambda(t) = P(t < T \leq t + \Delta | T > t) / \Delta, \text{ for small } \Delta$$

- ≈ the conditional probability that the event occurs in a short interval  $(t, t + \Delta]$ , given that it does not occur before  $t$ , divided by interval length.

In other words, during a short interval

$$\text{risk of event} \approx \text{hazard} \times \text{interval length}$$

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## Distribution concepts: survival and cumulative hazard functions

### Survival function

$$S(t) = P(T > t),$$

= probability of avoiding the event at least up to  $t$  (the event occurs only after  $t$ ).

The **cumulative hazard** (or integrated intensity):

$$\Lambda(t) = \int_0^t \lambda(u) du$$

Connections between the functions:

$$S(t) = \exp\{-\Lambda(t)\}$$

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## Observed data on survival times

For individuals  $i = 1, \dots, n$  let

$T_i$  = time to outcome event,

$U_i$  = time to censoring.

Censoring is assumed **noninformative**, i.e. independent from occurrence of events.

We observe

$y_i = \min\{T_i, U_i\}$ , i.e. the exit time, and

$\delta_i = 1_{\{T_i < U_i\}}$ , indicator (1/0) for the outcome event occurring first, before censoring.

Censoring must properly be taken into account in the statistical analysis.

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## Approaches for analysing survival time

- **Parametric model** (like Weibull, gamma, etc.) on hazard rate  $\lambda(t) \rightarrow$  Likelihood:

$$L = \prod_{i=1}^n \lambda(y_i)^{\delta_i} S(y_i)$$

- **Piecewise constant rate** model on  $\lambda(t)$ 
  - see Bendix's lecture on time-splitting (Poisson likelihood).
- **Non-parametric** methods, like Kaplan–Meier (KM) estimator of survival curve  $S(t)$  and Cox proportional hazards model on  $\lambda(t)$ .

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## R package survival

Tools for analysis with one outcome event.

- ▶ `Surv(time, event) -> sobj`  
creates a **survival object** `sobj` assuming that all start at 0, containing pairs  $(y_i, \delta_i)$ ,
- ▶ `Surv(entry, exit, event) -> sobj2`  
creates a survival object from entry and exit times,
- ▶ `survfit(sobj ~ x) -> sfo`  
creates a **survfit** object `sfo` containing KM or other non-parametric estimates (also from a fitted Cox model),
- ▶ `plot(sfo)`  
plot method for survival curves and related graphs,
- ▶ `coxph(sobj ~ x1 + x2)`  
fits a Cox model with covariates `x1` and `x2`.
- ▶ `survreg()` – parametric survival models.

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## Ex. Oral cancer data (cont'd)

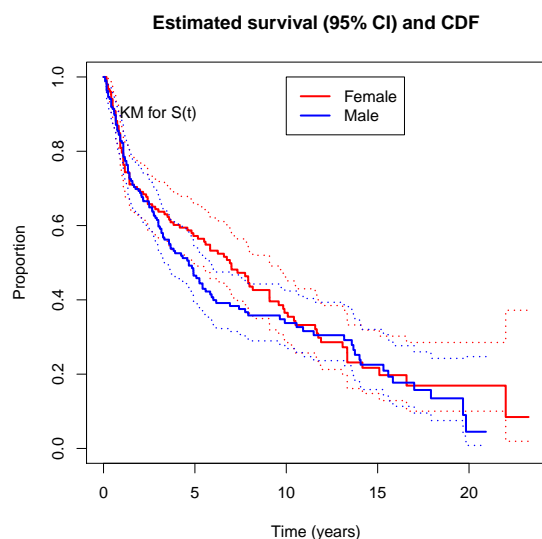
```
> orca$suob <- Surv(orca$time, 1*(orca$event > 0) )
> orca$suob[1:7] # + indicates censored observation
[1] 5.081+ 0.419 7.915 2.480 2.500 0.167 5.925+
> km1 <- survfit( suob ~ 1, data = orca)
> km1 # brief summary
Call: survfit(formula = suob ~ 1, data = orca)

      n  events  median 0.95LCL 0.95UCL 
338.00  229.00   5.42    4.33    6.92 
> summary(km1) # detailed KM-estimate
Call: survfit(formula = suob ~ 1, data = orca)

      time n.risk n.event survival std.err lower 95% CI upper 95% CI
0.085    338      2  0.9941 0.00417  0.9859      1.000
0.162    336      2  0.9882 0.00588  0.9767      1.000
0.167    334      4  0.9763 0.00827  0.9603      0.993
0.170    330      2  0.9704 0.00922  0.9525      0.989
0.246    328      1  0.9675 0.00965  0.9487      0.987
0.249    327      1  0.9645 0.01007  0.9450      0.984
0.252    326      3  0.9556 0.01120  0.9339      0.978
0.329    323      1  0.9527 0.01155  0.9303      0.976
0.334    322      1  0.9497 0.01189  0.9267      0.973
0.413    321      1  0.9467 0.01221  0.9231      0.971
0.419    320      6  0.9290 0.01397  0.9020      0.957
0.496    314      2  0.9231 0.01449  0.8951      0.952
```

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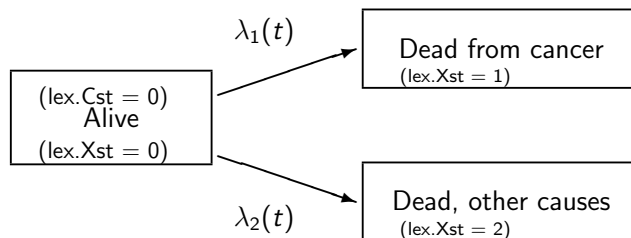
## Oral cancer: Kaplan-Meier estimates



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## Competing risks model: causes of death

- Often the interest is focused on the risk or hazard of dying from one specific cause.
- That cause may eventually not be realized, because a **competing cause** of death hits first.



- Generalizes to several competing causes.

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## Competing events & competing risks

In many epidemiological and clinical contexts there are competing events that may occur before the target event and remove the person from the population at risk for the event, e.g.

- *target event*: occurrence of endometrial cancer,  
*competing events*: hysterectomy or death.
- *target event*: relapse of a disease (ending the state of remission),  
*competing event*: death while still in remission.
- *target event*: divorce,  
*competing event*: death of either spouse.

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## Event-specific quantities

**Cumulative incidence function (CIF)** or

$$F_c(t) = P(T \leq t \text{ and } C = c), \quad c = 1, 2,$$

From these one can recover

- $F(t) = \sum_c F_c(t)$ , CDF of event-free survival time  $T$ , i.e. cumulative risk of any event by  $t$ .
- $S(t) = 1 - F(t)$ , **event-free survival function**, i.e. probability of avoiding all events by  $t$ , but  $S(t) \neq F_1(t) + F_2(t)$

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## Event-specific quantities (cont'd)

**Event- or cause-specific hazard function**

$$\begin{aligned}\lambda_c(t) &= \lim_{\Delta \rightarrow 0} \frac{P(t < T \leq t + \Delta \text{ and } C = c \mid T > t)}{\Delta} \\ &= \frac{f_c(t)}{1 - F(t)}\end{aligned}$$

CIF = risk of event  $c$  over risk period  $[0, t]$  in the presence of competing risks, also obtained

$$F_c(t) = \int_0^t \lambda_c(v) S(v) dv, \quad c = 1, 2,$$

More on the technical definitions of relevant quantities:

<http://bendixcarstensen.com/AdvCoh/papers/fundamentals.pdf>

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## Warning of “net risk” and “cause-specific survival”

- ▶ The “**net risk**” of outcome  $c$  by time  $t$ , assuming hypothetical elimination of competing risks, is often defined as

$$F_1^*(t) = 1 - S_1^*(t) = 1 - \exp\{-\Lambda_1(t)\} \neq S(t)$$

- ▶ In clinical survival studies, function  $S_1^*(t)$  is often called “**cause-specific survival**”, or “**net survival**”
- ▶ Yet, these \*-functions,  $F_1^*(t)$  and  $S_1^*(t)$ , lack proper probability interpretation when competing risks exist.
- ▶ Hence, their use should be viewed critically (Andersen & Keiding, *Stat Med*, 2012)

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## Analysis with competing events

Let  $U_i$  = censoring time,  $T_i$  = time to first event, and  $C_i$  = variable for event 1 or 2. We observe

- ▶  $y_i = \min\{T_i, U_i\}$ , i.e. the exit time, and
- ▶  $\delta_{ic} = 1_{\{T_i < U_i \text{ \& } C_i = c\}}$ , indicator (1/0) for event  $c$  being first observed,  $c = 1, 2$ .

Non-parametric estimation of CIF

- ▶ Let  $t_1 < t_2 < \dots < t_K$  be the  $K$  distinct time points at which any outcome event was observed, Let also  $\hat{S}(t)$  be KM estimator for overall  $S(t)$ .
- ▶ **Aalen-Johansen estimator** (AJ) for the cumulative incidence function  $F(t)$  should be used

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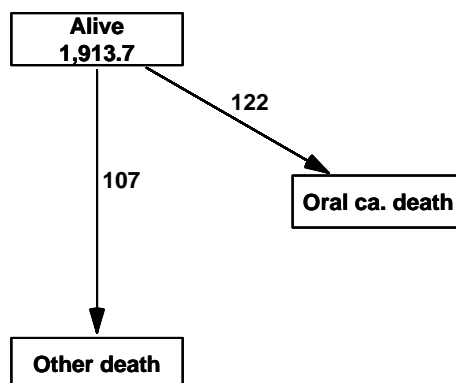
## R tools for competing risks analysis

- ▶ `survfit( Surv(...,type="mstate") )` in Survival-package can be fitted for any transition of a multistate model and to obtain A-J estimates.
- ▶ Package `cmprsk` – `cuminc(ftime, fstatus, ...)` computes CIF-estimates, and can be compared in more than two samples. `plot.cuminc()` plots them.
- ▶ Package `Epi` – Lexis tools for multistate analyses  
Will be advertised by Bendix!

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## Box diagram for transitions

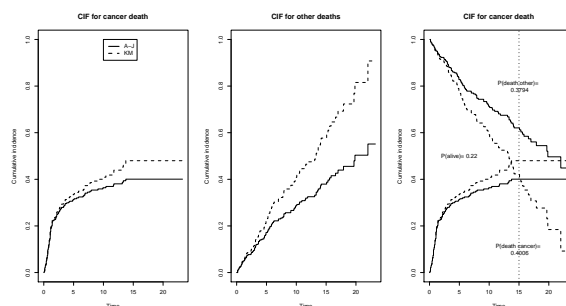
NOTE: `entry.status` has been set to "Alive" for all.  
NOTE: `entry` is assumed to be 0 on the stime timescale.



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## Ex. Survival from oral cancer

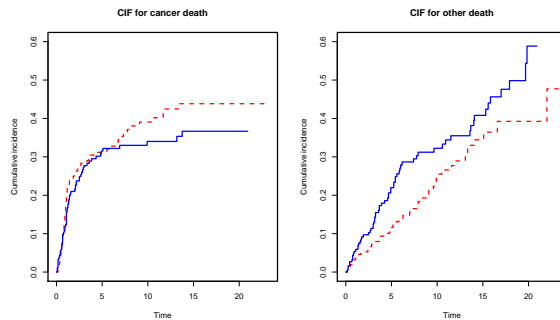
- ▶ AJ-estimates of CIFs (solid) for both causes.
- ▶ Naive KM-estimates of CIF (dashed) > AJ-estimates
- ▶ CIF curves may also be stacked (right).



**NB.** The sum of the naive KM-estimates of CIF exceeds 100% at 13 years!

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## Ex. CIFs by cause in men and women



CIF for cancer higher in women (chance?) but for other causes higher in men (no surprise).

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## Regression models for time-to-event data

Regression models for hazards can be defined e.g. for

(a) hazards, multiplicatively:

$$\lambda_i(t) = \lambda_0(t; \alpha) r(\eta_i), \quad \text{where}$$

$\lambda_0(t; \alpha)$  = baseline hazard and

$r(\eta_i)$  = relative rate function, typically  $\exp(\eta_i)$

(b) hazards, additively:

$$\lambda_i(t) = \lambda_0(t; \alpha) + \eta_i.$$

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## Relative hazards model or Cox model

In model (b), the baseline hazard  $\lambda_0(t, \alpha)$  may be given a parametric form (e.g. Weibull) or a piecewise constant rate (exponential) structure.

Often a parameter-free form  $\lambda_0(t)$  is assumed. Then

$$\lambda_i(t) = \lambda_0(t) \exp(\eta_i),$$

specifies the **Cox model** or the **semiparametric proportional hazards model**.

$\eta_i = \beta_1 x_{i1} + \dots + \beta_p x_{ip}$  not depending on time.

Generalizations: **time-dependent** covariates  $x_{ij}(t)$

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## PH model: interpretation of parameters

Present the model explicitly in terms of  $x$ 's and  $\beta$ 's.

$$\lambda_i(t) = \lambda_0(t) \exp(\beta_1 x_{i1} + \dots + \beta_p x_{ip})$$

Consider two individuals,  $i$  and  $i'$ , having the same values of all other covariates except the  $j^{\text{th}}$  one.

The ratio of hazards is constant:

$$\frac{\lambda_i(t)}{\lambda_{i'}(t)} = \frac{\exp(\eta_i)}{\exp(\eta_{i'})} = \exp\{\beta_j(x_{ij} - x_{i'j})\}.$$

Thus  $e^{\beta_j} = \text{HR}_j = \mathbf{hazard\ ratio}$  or relative rate associated with a unit change in covariate  $X_j$ .

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## Ex. Total mortality of oral ca. patients

Fitting Cox models with sex and sex + age.

```
> cm0 <- coxph( suob ~ sex, data = orca)
> summary( cm0)
      coef exp(coef) se(coef)      z Pr(>|z|)
sexMale 0.126    1.134    0.134  0.94   0.35
      exp(coef) exp(-coef) lower .95 upper .95
sexMale      1.13      0.882   0.872   1.47

> cm1 <- coxph( suob ~ sex + age, data = orca)
> summary(cm1)
      exp(coef) exp(-coef) lower .95 upper .95
sexMale      1.49      0.669   1.14   1.96
age         1.04      0.960   1.03   1.05
```

The M/F contrast visible only after age-adjustment.

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## Predictions from the Cox model

- Individual survival *times* cannot be predicted but ind'l survival *curves* can. PH model implies:

$$S_i(t) = [S_0(t)]^{\exp(\beta_1 x_{i1} + \dots + \beta_p x_{ip})}$$

- Having estimated  $\beta$  by partial likelihood, the baseline  $S_0(t)$  is estimated by Breslow method
- From these, a survival curve for an individual with given covariate values is predicted.
- In R: `pred <- survfit(mod, newdata=...)` and `plot(pred)`, where `mod` is the fitted `coxph` object, and `newdata` specifies the covariate values. `newdata` is always needed for predictions.

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## Modelling with competing risks

Main options, providing answers to different questions.

- (a) Cox model for event-specific hazards

$\lambda_c(t) = f_c(t)/[1 - F(t)]$ , when e.g. the interest is in the biological effect of the prognostic factors on the fatality of the very disease that often leads to the relevant outcome.

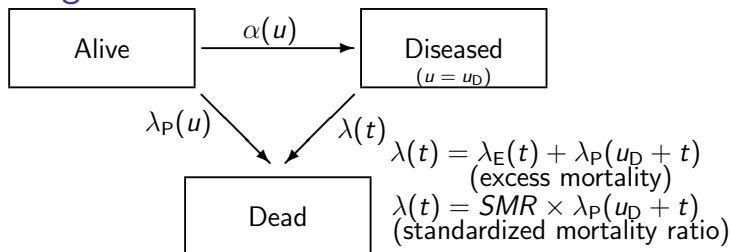
- (b) **Fine–Gray model** for the hazard of the subdistribution

$\gamma_c(t) = f_c(t)/[1 - F_c(t)]$  when we want to assess the impact of the factors on the overall cumulative incidence of event  $c$ .

– Function `crr()` in package `cmprsk`.

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## Competing risks model: excess hazard of death



where

- ▶  $\lambda_P(u)$  is the hazard of dying from any cause among disease-free members
- ▶  $\lambda_E(t)$  is the excess hazard of dying from the disease among diseased cohort members

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# Representation of follow-up

**Bendix Carstensen** Steno Diabetes Center Copenhagen  
Gentofte, Denmark  
<http://BendixCarstensen.com>

SPE, Tartu, Estonia,

August 2019

<http://BendixCarstensen.com/SPE>

From /home/bendix/teach/SPE/git/SPE/lectures/time-rep/time-rep.tex

Sunday 18<sup>th</sup> August, 2019, 13:47

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# Representation of follow-up

**Bendix Carstensen**

Representation of follow-up

SPE, Tartu, Estonia,

August 2019

<http://BendixCarstensen.com/SPE>

time-split

- ▶ In follow-up studies we estimate rates from:
  - ▶  $D$  — events, deaths
  - ▶  $Y$  — person-years
  - ▶  $\hat{\lambda} = D/Y$  rates
  - ▶ ... empirical counterpart of intensity — an **estimate**
- ▶ Rates differ between persons.
- ▶ Rates differ **within** persons:
  - ▶ by age
  - ▶ by calendar time
  - ▶ by disease duration
  - ▶ ...
- ▶ Multiple timescales.
- ▶ Multiple states (little boxes — later)



## 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 pieces of information recorded:

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

These are specific for each **type** of outcome.

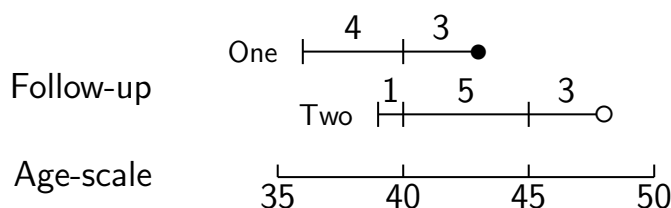
Representation of follow-up (time-split)

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## Stratification by age

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

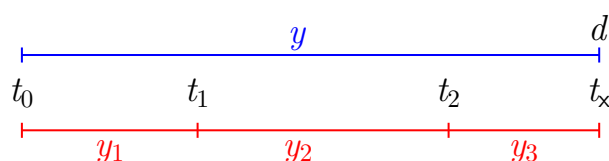
If follow-up is long, stratification by categories of **current age** is preferable.



- allowing rates to vary across age-bands
- how do we do the split and why is it OK?

Representation of follow-up (time-split)

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Probability

$$P(d \text{ at } t_x | \text{entry } t_0)$$

$$= P(\text{surv } t_0 \rightarrow t_1 | \text{entry } t_0)$$

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

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

log-Likelihood

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

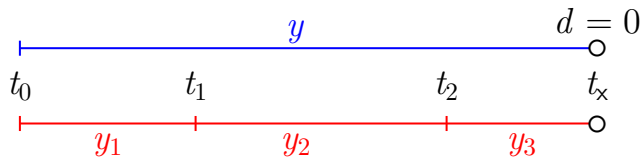
$$= 0 \log(\lambda) - \lambda y_1$$

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

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

Representation of follow-up (time-split)

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Probability

$$P(\text{surv } t_0 \rightarrow t_x | \text{entry } t_0)$$

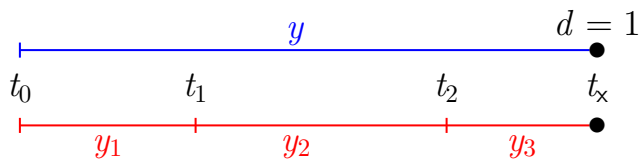
$$= P(\text{surv } t_0 \rightarrow t_1 | \text{entry } t_0) \\ \times P(\text{surv } t_1 \rightarrow t_2 | \text{entry } t_1) \\ \times P(\text{surv } t_2 \rightarrow t_x | \text{entry } t_2)$$

log-Likelihood

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

Representation of follow-up (time-split)

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Probability

$$P(\text{event at } t_x | \text{entry } t_0)$$

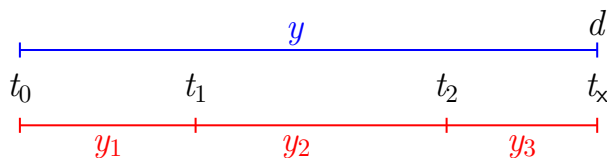
$$= P(\text{surv } t_0 \rightarrow t_1 | \text{entry } t_0) \\ \times P(\text{surv } t_1 \rightarrow t_2 | \text{entry } t_1) \\ \times P(\text{event at } t_x | \text{entry } t_2)$$

log-Likelihood

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

Representation of follow-up (time-split)

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Probability

$$P(d \text{ at } t_x | \text{entry } t_0)$$

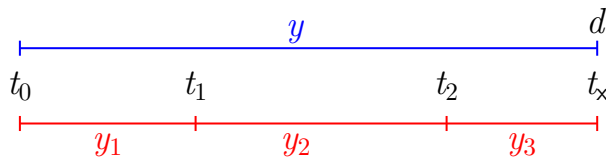
$$= P(\text{surv } t_0 \rightarrow t_1 | \text{entry } t_0) \\ \times P(\text{surv } t_1 \rightarrow t_2 | \text{entry } t_1) \\ \times P(d \text{ at } t_x | \text{entry } t_2)$$

log-Likelihood

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

Representation of follow-up (time-split)

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Probability

log-Likelihood

$$P(d \text{ at } t_x | \text{entry } t_0)$$

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

$$= P(\text{surv } t_0 \rightarrow t_1 | \text{entry } t_0)$$

$$= 0 \log(\lambda_1) - \lambda_1 y_1$$

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

$$+ 0 \log(\lambda_2) - \lambda_2 y_2$$

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

$$+ d \log(\lambda_3) - \lambda_3 y_3$$

— allows different rates ( $\lambda_i$ ) in each interval

Representation of follow-up (time-split)

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## Dividing time into bands:

If we want to compute  $D$  and  $Y$  in intervals on some timescale we must decide on:

**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

Representation of follow-up (time-split)

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## 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.

Representation of follow-up (time-split)

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# Splitting the follow up

	subj. 1	subj. 2	subj. 3
Age at Entry:	13.06	18.44	4.54
Age at exit:	44.95	41.14	11.12
Status at exit:	Dead	Alive	Dead
<hr/>			
Y	31.89	22.70	6.58
D	1	0	1

Representation of follow-up (time-split)

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	subj. 1		subj. 2		subj. 3		$\Sigma$	
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
$\Sigma$	31.89	1	22.70	0	6.58	1	60.17	2

Representation of follow-up (time-split)

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# 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?

Representation of follow-up (time-split)

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## 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:

$(d, y)$       (**event**, **duration**)

- ▶ **Covariates** in analysis of rates:
  - ▶ **timescales**
  - ▶ other (fixed) measurements
- ▶ ...do not confuse **duration** and **timescale** !

Representation of follow-up (time-split)

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## Follow-up data in Epi — Lexis objects I

```
> thoro[1:6,1:8]
```

	id	sex	birthdat	contrast	injecdat	volume	exitdat	exitstat
1	1	2	1916.609	1	1938.791	22	1976.787	1
2	2	2	1927.843	1	1943.906	80	1966.030	1
3	3	1	1902.778	1	1935.629	10	1959.719	1
4	4	1	1918.359	1	1936.396	10	1977.307	1
5	5	1	1902.931	1	1937.387	10	1945.387	1
6	6	2	1903.714	1	1937.316	20	1944.738	1

Timescales of interest:

- ▶ Age
- ▶ Calendar time
- ▶ Time since injection

Representation of follow-up (time-split)

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## Follow-up data in Epi — Lexis objects II

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

NOTE: entry.status has been set to 0 for all.

NOTE: Dropping 2 rows with duration of follow up < tol

```
> summary( thL )
```

Transitions:

To

From	0	1	Records:	Events:	Risk time:	Persons:	
	0	504	1964	2468	1964	51934.08	2468

Representation of follow-up (time-split)

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## Definition of Lexis object

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

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

$\text{exitdat} - \text{injecdat}$

One element of entry and exit must have same name (**dte**).

Representation of follow-up (time-split)

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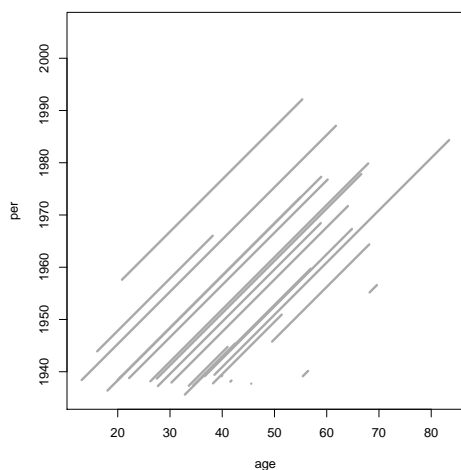
## The looks of a Lexis object

```
> thL[1:4,1:9]
  age      dte 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:
  0 504 1964    2468    1964    51934.08    2468
```

Representation of follow-up (time-split)

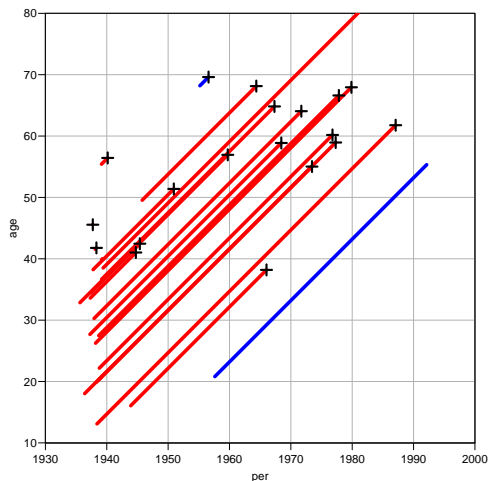
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```
> plot( thL, lwd=3 )
```

Representation of follow-up (time-split)

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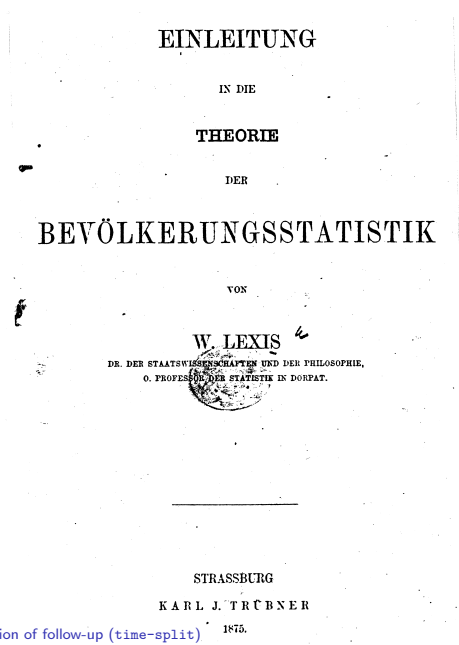


## Lexis diagram

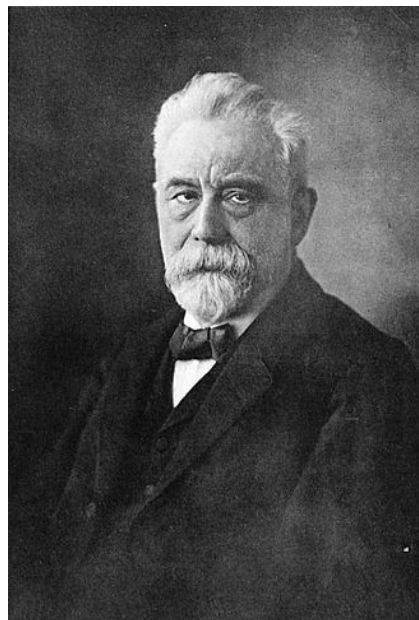
```
> plot( thL, 2:1, lwd=5, col=c("red","blue")[thL$contrast],
+       grid=TRUE, lty.grid=1, col.grid=gray(0.7),
+       xlim=1930+c(0,70), xaxs="i", ylim= 10+c(0,70), yaxs="i", las=1 )
> points( thL, 2:1, pch=c(NA,3)[thL$lex.Xst+1],lwd=3, cex=1.5 )
```

Representation of follow-up (time-split)

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Representation of follow-up (time-split)



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## Splitting follow-up time

```
> spl1 <- splitLexis( thL, time.scale="age", breaks=seq(0,100,20) )
> round(spl1,1)
  age   dte   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
...
```

Representation of follow-up (time-split)

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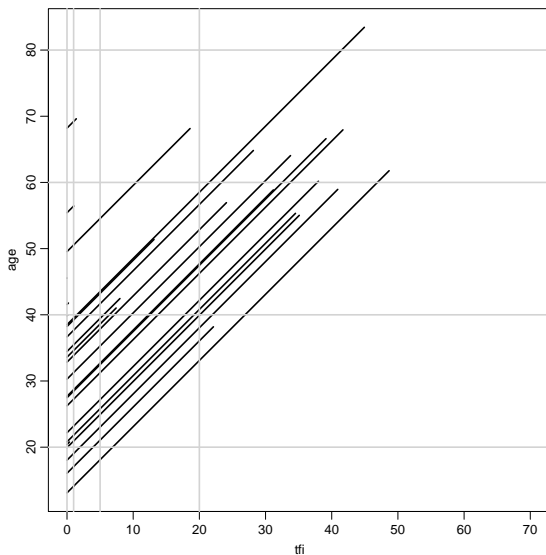
## Split on another timescale

```
> spl2 <- splitLexis( spl1, time.scale="tfi", breaks=c(0,1,5,20,100) )
> round( spl2, 1 )
```

	lex.id	age	dte	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

Representation of follow-up (time-split)

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```
plot( spl2, c(1,3), col="black", lwd=2 )
```

Representation of follow-up (time-split)

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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

## Splitting on several timescales

```
> spl1 <- splitLexis( thL , time.scale="age", breaks=seq(0,100,20) )
> spl2 <- splitLexis( spl1, time.scale="tfi", breaks=c(0,1,5,20,100) )
> summary( spl2 )
```

Transitions:

To

From	0	1	Records:	Events:	Risk time:	Persons:
0	8250	1964	10214	1964	51934.08	2468

```
> library(popEpi)
> splx <- splitMulti( thL , age=seq(0,100,20), tfi=c(0,1,5,20,100) )
> summary( splx )
```

Transitions:

To

From	0	1	Records:	Events:	Risk time:	Persons:
0	8248	1964	10212	1964	51916.98	2468

```
> # NOTE: splitMulti excludes follow-up outside range of breaks
```

Representation of follow-up (time-split)

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## Likelihood for time-split data

- ▶ The 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 the likelihood.
- ▶ Each term looks like a contribution from a Poisson variate (albeit with values only 0 or 1)
- ▶ Rates can vary along several timescales simultaneously.
- ▶ Models can include fixed covariates, as well as the timescales (the left end-points of the intervals) as continuous variables.
- ▶ The latter is where we will need splines.

Representation of follow-up (time-split)

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## Analysis of time-split data

Observations classified by  $p$ —person and  $i$ —interval

- ▶  $d_{pi}$  — events in the variable: `lex.Xst`
- ▶  $y_{pi}$  — risk time: `lex.dur` (duration)
- ▶ Covariates are:
  - ▶ timescales (age, period, time in study)
  - ▶ other variables for this person (constant in each interval).
- ▶ Model rates using the covariates in `glm`:
  - no difference between time-scales and other covariates.

Representation of follow-up (time-split)

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## Fitting a simple model

```
> stat.table( contrast,
+             list( D = sum( lex.Xst ),
+                   Y = sum( lex.dur ),
+                   Rate = ratio( lex.Xst, lex.dur, 100 ) ),
+             margin = TRUE,
+             data = spl2 )
```

contrast	D	Y	Rate
1	928.00	20094.74	4.62
2	1036.00	31839.35	3.25
Total	1964.00	51934.08	3.78

Representation of follow-up (time-split)

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## Fitting a simple model

contrast	D	Y	Rate
1	928.00	20094.74	4.62
2	1036.00	31839.35	3.25

```
> m0 <- glm( (lex.Xst==1) ~ factor(contrast) - 1,
+           offset = log(lex.dur/100),
+           family = poisson,
+           data = spl2 )
> round( ci.exp( m0 ), 2 )
```

```
              exp(Est.) 2.5% 97.5%
factor(contrast)1      4.62 4.33  4.93
factor(contrast)2      3.25 3.06  3.46
```

... a Poisson model for mortality using log-peron-years as offset

Representation of follow-up (time-split)

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## Fitting a simple model

contrast	D	Y	Rate
1	928.00	20094.74	4.62
2	1036.00	31839.35	3.25

```
> m0 <- glm( cbind(lex.Xst,lex.dur/100) ~ factor(contrast) - 1,
+           family = poisreg,
+           data = spl2 )
> round( ci.exp( m0 ), 2 )
```

```
              exp(Est.) 2.5% 97.5%
factor(contrast)1      4.62 4.33  4.93
factor(contrast)2      3.25 3.06  3.46
```

... a Poisson model for mortality rates based on deaths and person-years

Representation of follow-up (time-split)

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## Fitting a simple model — aggregate data

contrast	D	Y	Rate
1	928.00	20094.74	4.62
2	1036.00	31839.35	3.25

As long as we only use covariates that take only a few values, we can model the aggregate data directly:

```
> mx <- glm( cbind( c(928,1036), c(20094.74,31839.35)/100 ) ~ factor(1:2) - 1,
+           family=poisreg )
> round( ci.exp( mx ), 2 )
```

```
              exp(Est.) 2.5% 97.5%
factor(1:2)1      4.62 4.33  4.93
factor(1:2)2      3.25 3.06  3.46
```

Representation of follow-up (time-split)

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# SMR

## Bendix Carstensen

Representation of follow-up

SPE, Tartu, Estonia,

August 2019

<http://BendixCarstensen.com/SPE>

SMR

## Cohorts where all are exposed

When there is no comparison group we may ask:

Do mortality rates in cohort differ from those of an **external** population, for example:

Rates from:

- ▶ Occupational cohorts
- ▶ Patient cohorts

compared with reference rates obtained from:

- ▶ Population statistics (mortality rates)
- ▶ Hospital registers (disease rates)

SMR (SMR)

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## Cohort rates vs. population rates: RSR

- ▶ **Additive:**  $\lambda(a) = \delta(a) + \lambda_{\text{pop}}(a)$
- ▶ Note that the survival (since  $a = a_0$ , say) is:

$$\begin{aligned} S(a) &= \exp\left(-\int_{a_0}^a \delta(a) + \lambda_{\text{pop}}(a) \, da\right) \\ &= \exp\left(-\int_{a_0}^a \delta(a) \, da\right) \times S_{\text{pop}}(a) \\ \Rightarrow \quad r(a) &= S(a)/S_{\text{pop}}(a) = \exp\left(-\int_{a_0}^a \delta(a) \, da\right) \end{aligned}$$

- ▶ **Additive** model for **rates**  $\Leftrightarrow$  **Relative survival** model.

SMR (SMR)

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## Cohort rates vs. population rates: SMR

- ▶ **Multiplicative:**  $\lambda(a) = \theta \times \lambda_{\text{pop}}(a)$
- ▶  $D_a$  deaths during  $Y_a$  person-years an age-band  $a$  gives the likelihood:

$$D_a \log(\lambda(a)) - \lambda(a) Y_a = D_a \log(\theta \lambda_{\text{pop}}(a)) - \theta \lambda_{\text{pop}}(a) Y_a$$

- ▶  $\lambda_{\text{pop}}(a) Y_a = E_a$  is the "expected" number of cases in age  $a$ , so the log-likelihood contribution from age  $a$  is:

$$D_a \log(\theta) - \theta (\lambda_{\text{pop}}(a) Y_a) = D_a \log(\theta) - \theta (E_a)$$

- ▶ The log-likelihood is similar to the log-likelihood for a rate, so:

$$\hat{\theta} = \sum_a D_a / \sum_a E_a = \text{Observed/Expected} = \text{SMR}$$

SMR (SMR)

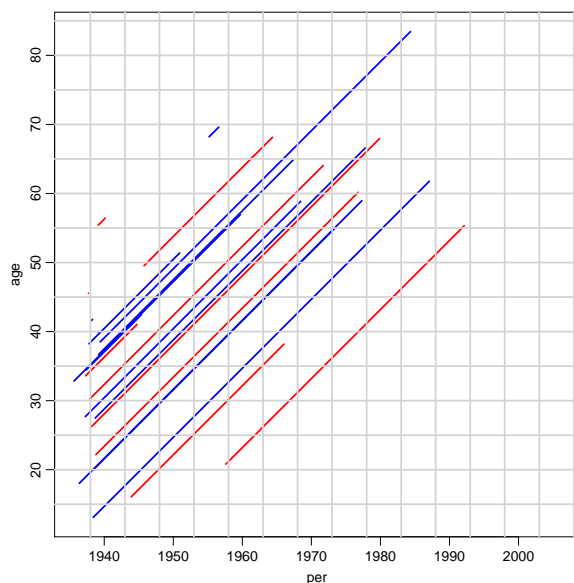
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## Modelling the SMR in practise

- ▶ As for the rates, the SMR can be modelled using individual data.
- ▶ Response is  $d_i$ , the event indicator (`lex.Xst`).
- ▶ log-offset is the expected value for each piece of follow-up,  $e_i = y_i \times \lambda_{\text{pop}}$  (`lex.dur * rate`)
- ▶  $\lambda_{\text{pop}}$  is the population rate corresponding to the age, period and sex of the follow-up period  $y_i$ .

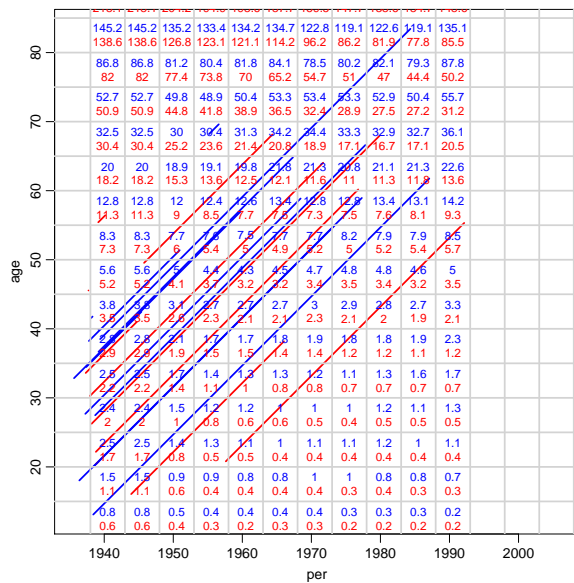
SMR (SMR)

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SMR (SMR)

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SMR (SMR)

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## Split the data to fit with population data

```
> thad <- splitMulti(thL, age=seq(0,90,5), dte=seq(1938,2038,5) )
> summary( thad )
```

Transitions:

To

```
From      0      1  Records:  Events: Risk time:  Persons:
0 21059 1939      22998      1939      51787.96      2463
```

## Create variables to fit with the population data

```
> thad$agr <- timeBand( thad, "age", "left" )
> thad$per <- timeBand( thad, "dte", "left" )
> round( thad[1:5,c("lex.id","age","agr","dte","per","lex.dur","lex.Xst","sex")],
```

	lex.id	age	agr	dte	per	lex.dur	lex.Xst	sex
1:	1	22.18	20	1938.79	1938	2.82	0	2
2:	1	25.00	25	1941.61	1938	1.39	0	2
3:	1	26.39	25	1943.00	1943	3.61	0	2
4:	1	30.00	30	1946.61	1943	1.39	0	2
5:	1	31.39	30	1948.00	1948	3.61	0	2

SMR (SMR)

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```
> data( gmortDK )
> dim( gmortDK )

[1] 418  21

> gmortDK[1:6,1:6]

  agr per sex  risk    dt    rt
1   0  38   1 996019 14079 14.135
2   5  38   1 802334   726  0.905
3  10  38   1 753017   600  0.797
4  15  38   1 773393  1167  1.509
5  20  38   1 813882  2031  2.495
6  25  38   1 789990  1862  2.357

> gmortDK$per <- gmortDK$per+1900
> #
> thadx <- merge( thad, gmortDK[,c("agr","per","sex","rt")] )
> #
> thadx$E <- thadx$lex.dur * thadx$rt / 1000
```

SMR (SMR)

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```
> stat.table( contrast,
+             list( D = sum( lex.Xst ),
+                   Y = sum( lex.dur ),
+                   E = sum( E ),
+                   SMR = ratio( lex.Xst, E ) ),
+             margin = TRUE,
+             data = thadx )
```

contrast	D	Y	E	SMR
1	917.00	20045.46	214.66	4.27
2	1022.00	31742.51	447.21	2.29
Total	1939.00	51787.96	661.87	2.93

SMR (SMR)

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contrast	D	Y	E	SMR
1	917.00	20045.46	214.66	4.27
2	1022.00	31742.51	447.21	2.29

```
> m.SMR <- glm( cbind(lex.Xst,E) ~ factor(contrast) - 1,
+              family = poisreg,
+              data = thadx )
> round( ci.exp( m.SMR ), 2 )
```

```
              exp(Est.) 2.5% 97.5%
factor(contrast)1      4.27 4.00  4.56
factor(contrast)2      2.29 2.15  2.43
```

- Analysis of SMR is like analysis of rates:
- Replace  $Y$  with  $E$  — that's all!
- ...it's the calculation of  $E$  that is difficult

SMR (SMR)

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# Nested case-control and case-cohort studies

Tuesday, 27 August, 2019

Esa Läärä & Martyn Plummer

Statistical Practice in Epidemiology with R  
University of Tartu, Estonia  
23 to 28 August, 2019

## Points to be covered

- ▶ Outcome-dependent sampling designs a.k.a. **case-control** studies vs. **full cohort** design.
- ▶ **Nested case-control** study (NCC): sampling of controls from risk-sets during follow-up of study population.
- ▶ **Matching** in selection of control subjects in NCC.
- ▶ R tools for NCC: function `ccwc()` in `Epi` for sampling controls, and `clogit()` in `survival` for model fitting.
- ▶ **Case-cohort** study (CC): sampling a subcohort from the whole cohort as it is at the start of follow-up.
- ▶ R tools for CC model fitting: function `cch()` in `survival`

Nested case-control and case-cohort studies

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## Example: Smoking and cervix cancer

Study population, measurements, follow-up, and sampling design

- ▶ Joint cohort of  $N \approx 500\,000$  women from 3 Nordic biobanks.
- ▶ Follow-up: From variable entry times since 1970s till 2000.
- ▶ For each of 200 cases, 3 controls were sampled; matched for biobank, age ( $\pm 2$  y), and time of entry ( $\pm 2$  mo).
- ▶ Frozen sera of cases and controls analyzed for cotinine etc.

Main result: Adjusted OR = 1.5 (95% CI 1.1 to 2.3) for high ( $>242.6$  ng/ml) vs. low ( $<3.0$  ng/ml) cotinine levels.

Simen Kapeu *et al.* (2009) *Am J Epidemiol*

Nested case-control and case-cohort studies

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## Example: USF1 gene and CVD

Study population, measurements, follow-up, and sampling design

- ▶ Two FINRISK cohorts, total  $N \approx 14000$  M & F, 25-64 y.
- ▶ Baseline health exam, questionnaire & blood specimens at recruitment in the 1990s – Follow-up until the end of 2003.
- ▶ Subcohort of 786 subjects sampled.
- ▶ 528 incident cases of CVD; 72 of them in the subcohort.
- ▶ Frozen blood from cases and subcohort members genotyped.

Main result: Female carriers of a high risk haplotype had a 2-fold hazard of getting CVD [95% CI: 1.2 to 3.5]

Komulainen *et al.* (2006) *PLoS Genetics*

Nested case-control and case-cohort studies

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## Full cohort design & its simple analysis

- ▶ **Full cohort design:** Data on exposure variables obtained for all subjects in a large study population.
- ▶ Summary data for crude comparison:

	Exposed	Unexposed	Total
Cases	$D_1$	$D_0$	$D$
Non-cases	$B_1$	$B_0$	$B$
Group size at start	$N_1$	$N_0$	$N$
Follow-up times	$Y_1$	$Y_0$	$Y$

- ▶ Crude estimation of **hazard ratio**  $\rho = \lambda_1/\lambda_0$ :  
**incidence rate ratio** IR, with standard error of  $\log(\text{IR})$ :

$$\hat{\rho} = \text{IR} = \frac{D_1/Y_1}{D_0/Y_0} \quad \text{SE}[\log(\text{IR})] = \sqrt{\frac{1}{D_1} + \frac{1}{D_0}}.$$

- ▶ More refined analyses: Poisson or Cox regression.

Nested case-control and case-cohort studies

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## Problems with full cohort design

Obtaining exposure and covariate data

- ▶ Slow and expensive in a big cohort.
- ▶ Easier with questionnaire and register data,
- ▶ Extremely costly and laborious for *e.g.*
  - measurements from biological specimens, like genotyping, antibody assays, *etc.*
  - dietary diaries & other manual records

*Can we obtain equally valid estimates of hazard ratios etc. with nearly as good precision by some other strategies?*

Yes – we can!

Nested case-control and case-cohort studies

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## Estimation of hazard ratio

The incidence rate ratio can be expressed:

$$\begin{aligned} \text{IR} &= \frac{D_1/D_0}{Y_1/Y_0} = \frac{\text{cases: exposed / unexposed}}{\text{person-times: exposed / unexposed}} \\ &= \frac{\text{exp're odds in cases}}{\text{exp're odds in p-times}} = \text{exposure odds ratio (EOR)} \end{aligned}$$

= Exposure distribution in cases vs. that in cohort!

Implication for more efficient design:

- ▶ *Numerator*: Collect exposure data on all cases.
- ▶ *Denominator*: Estimate the ratio of person-times  $Y_1/Y_0$  of the exposure groups in the cohort by **sampling** “control” subjects, on whom exposure is measured.

Nested case-control and case-cohort studies

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## Case-control designs

General principle: Sampling of subjects from a given study population is *outcome-dependent*.

Data on risk factors are collected separately from

(I) **Case group**: All (or high % of) the  $D$  subjects in the study population (total  $N$ ) encountering the outcome event during the follow-up.

(II) **Control group**:

- ▶ Random **sample** (simple or stratified) of  $C$  subjects ( $C \ll N$ ) from the population.
- ▶ Eligible controls must be *at risk* (alive, under follow-up & free of outcome) at given time(s).

Nested case-control and case-cohort studies

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## Study population in a case-control study?

Ideally: The study population comprises subjects who would be included as cases, if they got the outcome in the study

- ▶ *Cohort-based studies*: **cohort** or **closed** population of well-identified subjects under intensive follow-up for outcomes (e.g. biobank cohorts).
- ▶ *Register-based studies*: **open** or **dynamic** population in a region covered by a disease register.
- ▶ *Hospital-based studies*: dynamic **catchment** population of cases – may be hard to identify (e.g. hospitals in US).

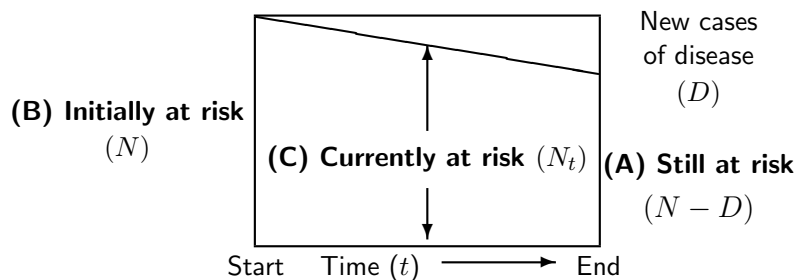
In general, the role of control subjects is to represent the distribution of person-times by exposure variables in the underlying population from which the cases emerge.

Nested case-control and case-cohort studies

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## Sampling of controls – alternative frames

Illustrated in a simple longitudinal setting:  
Follow-up of a cohort over a fixed risk period & no censoring.



Rodrigues, L. & Kirkwood, B.R. (1990). Case-control designs of common diseases ... *Int J Epidemiol* **19**: 205-13.

Nested case-control and case-cohort studies

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## Sampling schemes or designs for controls

### (A) Exclusive or traditional, “case-noncase” sampling

- ▶ Controls chosen from those  $N - D$  subjects still at risk (healthy) at the end of the risk period (follow-up).

### (B) Inclusive sampling or case-cohort design (CC)

- ▶ The control group – *subcohort* – is a random sample of the cohort ( $N$ ) at start.

### (C) Concurrent sampling or density sampling

- ▶ Controls drawn during the follow-up
- ▶ **Risk-set or time-matched sampling:**  
A set of controls is sampled from the risk set at each time  $t$  of diagnosis of a new case – a.k.a. **nested case-control design (NCC)**

Nested case-control and case-cohort studies

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## Nested case-control – two meanings

- ▶ In some epidemiologic books, the term “nested case-control study” (NCC) covers jointly all variants of sampling: **(A)**, **(B)**, and **(C)**, from a cohort.

Rothman *et al.* (2008): *Modern Epidemiology*, 3rd Ed.  
Dos Santos Silva (1999): *Cancer Epidemiology*. Ch 8-9

- ▶ In biostatistical texts NCC typically refers only to the variant of concurrent or density sampling **(C)**, in which *risk-set* or *time-matched* sampling is employed.

Borgan & Samuelsen (2003) in *Norsk Epidemiologi*  
Langholz (2005) in *Encyclopedia of Biostatistics*.

- ▶ We shall follow the biostatisticians!

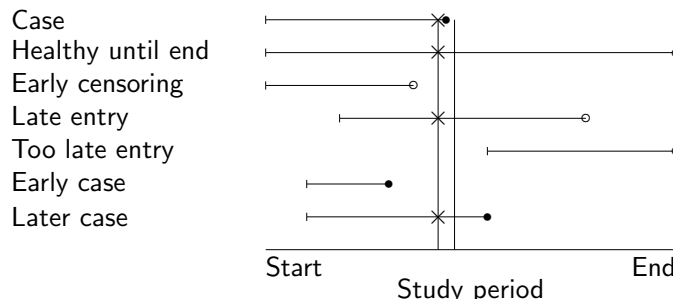
Nested case-control and case-cohort studies

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## NCC: Risk-set sampling with staggered entry

Sampling frame to select controls for a given case:

Members ( $\times$ ) of the **risk set** at  $t_k$ , i.e. the population at risk at the time of diagnosis  $t_k$  of case  $k$ .



**Sampled risk set** contains the case and the control subjects randomly sampled from the non-cases in the risk set at  $t_k$ .

Nested case-control and case-cohort studies

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## Use of different sampling schemes

(A) Exclusive sampling, or “textbook” case-control design

- ▶ Almost exclusively(!) used in studies of epidemics.
- ▶ (Studies on birth defects with *prevalent* cases.)

(B) Inclusive sampling or case-cohort design

- ▶ Good esp. for multiple outcomes, if measurements of risk factors from stored material remain stable.

(C) Concurrent or density sampling (without or with time-matching)

- ▶ The only logical design in an open population.
- ▶ Most popular in chronic diseases (Knol *et al.* 2008).

Designs (B) and (C) allow valid estimation of hazard ratios  $\rho$  without any “rare disease” assumption.

Nested case-control and case-cohort studies

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## Case-control studies: Textbooks vs. real life

- ▶ Many epi texts focus on the traditional design: **exclusive sampling** of controls, ignoring other designs.
- ▶ Claim: “*Odds ratio is the only estimable parameter.*”
- ▶ Yet, over 60% of published case-control studies apply **concurrent sampling** or **density sampling** of controls from an **open** or **dynamic** population.
- ▶ Thus, the parameter most often estimated is the **hazard ratio** (HR) or **rate ratio**  $\rho$ .
- ▶ Still, 90% of authors really estimating HR, reported as having estimated an OR (e.g. Simen Kapeu *et al.* 2009)

Knol *et al.* (2008). What do case-control studies estimate?

*Am J Epidemiol* **168**: 1073-81.

Nested case-control and case-cohort studies

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## Exposure odds ratio – estimate of what?

- Crude summary of case-control data

	exposed	unexposed	total
cases	$D_1$	$D_0$	$D$
controls	$C_1$	$C_0$	$C$

- Depending on study base & sampling strategy, the **exposure odds ratio**

$$\text{EOR} = \frac{D_1/D_0}{C_1/C_0} = \frac{\text{cases: exposed / unexposed}}{\text{controls: exposed / unexposed}}$$

is a consistent estimator of

- (a) hazard ratio, (b) risk ratio, (c) risk odds ratio,
- (d) prevalence ratio, or (e) prevalence odds ratio

- **NB.** In case-cohort studies with variable follow-up times  $C_1/C_0$  is substituted by  $\hat{Y}_1/\hat{Y}_0$ , from estimated p-years.

Nested case-control and case-cohort studies

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## Precision and efficiency

With exclusive **(A)** or concurrent **(C)** sampling of controls (unmatched), the estimated variance of  $\log(\text{EOR})$  is

$$\begin{aligned}\widehat{\text{var}}[\log(\text{EOR})] &= \frac{1}{D_1} + \frac{1}{D_0} + \frac{1}{C_1} + \frac{1}{C_0} \\ &= \text{cohort variance} + \text{sampling variance}\end{aligned}$$

- Depends basically on the numbers of cases, with  $\geq 4$  controls per case.
  - Is not much bigger than  $1/D_1 + 1/D_0 =$  variance in a full cohort study with same numbers of cases.
- ⇒ Usually  $< 5$  controls per case is enough.
- ⇒ *These designs are very cost-efficient!*

Nested case-control and case-cohort studies

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## Estimation in concurrent or density sampling

- Assume a simple situation: Prevalence of exposure in the study population stable over time.
- ⇒ The exposure odds  $C_1/C_0$  among controls
- = a consistent estimator of exposure odds  $Y_1/Y_0$  of person-times.
- Therefore, the crude  $\text{EOR} = (D_1/D_0)/(C_1/C_0)$
  - = a consistent estimator of hazard ratio  $\rho = \lambda_1/\lambda_0$ .
  - Variance of  $\log(\text{EOR})$  estimated as above.
  - Yet, stability of exposure distribution may be unrealistic, especially in a closed study population or cohort.
  - Solution: **Time-matched** sampling of controls from **risk sets**, i.e. NCC, & matched EOR to estimate HR.

Prentice & Breslow (1978), Greenland & Thomas (1982).

Nested case-control and case-cohort studies

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## Matching in case-control studies

- = **Stratified sampling** of controls, e.g. from the same region, sex, and age group as a given case
- ▶ **Frequency matching or group matching:**  
For cases in a specific stratum (e.g. same sex and 5-year age-group), a set of controls from a similar subgroup.
- ▶ **Individual matching** (1:1 or 1:m matching):  
For each case, choose 1 or more (rarely > 5) closely similar controls (e.g. same sex, age within  $\pm 1$  year).
- ▶ **NCC:** Sampling from risk-sets implies time-matching at least. Additional matching for other factors possible.
- ▶ **CC:** Subcohort selection involves no matching with cases.

Nested case-control and case-cohort studies

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## Virtues of matching

- ▶ Increases *efficiency*, if the matching factors are both
  - (i) strong *risk factors* of the disease, and
  - (ii) *correlated* with the main exposure.
- Major reason for matching.
- ▶ *Confounding* due to poorly quantified factors (sibship, neighbourhood, etc.) may be removed by close matching – only if properly analyzed.
- ▶ Biobank studies: Matching for storage time, freeze-thaw cycle & analytic batch improves **comparability of measurements** from frozen specimens
  - Match on the time of baseline measurements within the case's risk set.

Nested case-control and case-cohort studies

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## Warnings for overmatching

Matching a case with a control subject is a different issue than matching an unexposed subject to an exposed one in a cohort study – much trickier!

- ▶ Matching on an *intermediate* variable between exposure and outcome.
  - ⇒ *Bias!*
- ▶ Matching on a *surrogate* or *correlate* of exposure, which is not a true risk factor.
  - ⇒ *Loss of efficiency.*
- **Counter-matching:** Choose a control which is not similar to the case w.r.t a correlate of exposure.
  - ⇒ Increases efficiency!
  - Requires appropriate weighting in the analysis.

Nested case-control and case-cohort studies

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## Sampling matched controls for NCC using R

- ▶ Suppose key follow-up items are recorded for all subjects in a cohort, in which a NCC study is planned.
- ▶ Function `ccwc()` in package `Epi` can be used for risk-set sampling of controls. – Arguments:

```
entry : Time of entry to follow-up
exit  : Time of exit from follow-up
fail  : Status on exit (1 for case, 0 for censored)
origin : Origin of analysis time scale (e.g. time of birth)
controls : Number of controls to be selected for each case
match : List of matching factors
data  : Cohort data frame containing input variables
```

- ▶ Creates a data frame for a NCC study, containing the desired number of matched controls for each case.

Nested case-control and case-cohort studies

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## Analysis of matched studies

- ▶ Close matching induces a new parameter for each matched case-control set or stratum.  
⇒ **unconditional logistic regression** breaks down.
- ▶ Matching on well-defined variables (like age, sex)  
– include these factors as covariates.
- ▶ Matching on “soft” variables (like sibship) can be dealt with **conditional logistic regression**.
- ▶ Same method in matched designs **(A)**, exclusive, and **(C)**, concurrent, but interpretation of  $\beta_j$ s differs:

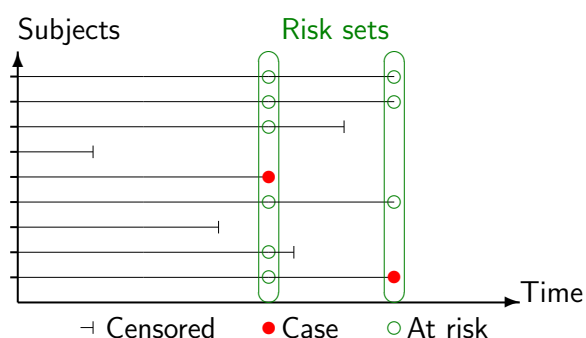
**(A)**  $\beta_j = \log$  of risk odds ratio (ROR),  
**(C)**  $\beta_j = \log$  of hazard ratio (HR).

Nested case-control and case-cohort studies

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## Full cohort design: Follow-up & risk sets

Each member of the cohort provides exposure data for all cases, as long as this member is at risk, *i.e.* (i) alive, (ii) not censored & (iii) free from outcome.



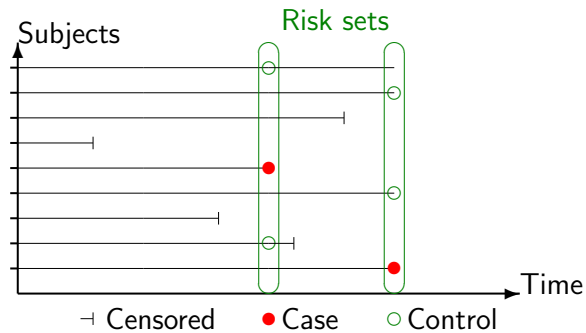
Times of new cases define the **risk-sets**.

Nested case-control and case-cohort studies

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## Nested case-control (NCC) design

Whenever a new case occurs, a set of controls (here 2/case) are sampled from its risk set.



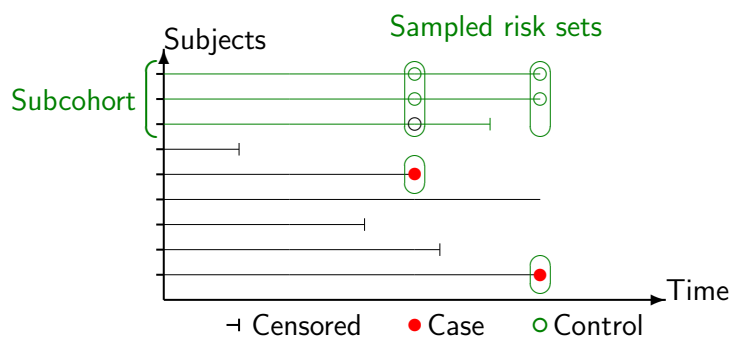
**NB.** A control once selected for some case can be selected as a control for another case, and can later on become a case, too.

Nested case-control and case-cohort studies

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## Case-cohort (CC) design

**Subcohort:** Sample of the whole cohort randomly selected at the outset.  
– Serves as a reference group for all cases.



**NB.** A subcohort member can become a case, too.

Nested case-control and case-cohort studies

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## Modelling in NCC and other matched studies

Cox proportional hazards model:

$$\lambda_i(t, x_i; \beta) = \lambda_0(t) \exp(x_{i1}\beta_1 + \dots + x_{ip}\beta_p),$$

Estimation: partial likelihood  $L^P = \prod_k L_k^P$ :

$$L_k^P = \exp(\eta_{i_k}) / \sum_{i \in \tilde{R}(t_k)} \exp(\eta_i),$$

where  $\tilde{R}(t_k)$  = **sampled risk set** at observed event time  $t_k$ , containing the case + sampled controls ( $t_1 < \dots < t_D$ )

⇒ Fit stratified Cox model, with  $\tilde{R}(t_k)$ 's as the strata.

⇔ **Conditional logistic regression**

– function `clogit()` in `survival`, wrapper of `coxph()`.

Nested case-control and case-cohort studies

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## Modelling case-cohort data

Cox's PH model  $\lambda_i(t) = \lambda_0(t) \exp(\eta_i)$  again, but ...

- ▶ Analysis of survival data relies on the theoretical principle that *you can't know the future*.
- ▶ Case-cohort sampling breaks this principle: cases are sampled based on what *is known* to be happening to them during follow-up.
- ▶ The union of cases and subcohort is a mixture
  1. random sample of the population, and
  2. "high risk" subjects who are *certain* to become cases.

⇒ Ordinary Cox partial likelihood is wrong.

- ▶ Overrepresentation of cases must be corrected for, by (I) **weighting**, or (II) **late entry method**.

Nested case-control and case-cohort studies

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## Correction method I – weighting

The method of **weighted partial likelihood** borrows some basics ideas from survey sampling theory.

- ▶ Sampled risk sets  
 $\tilde{R}(t_k) = \{\text{cases}\} \cup \{\text{subcohort members}\}$  at risk at  $t_k$ .
- ▶ Weights:
  - $w = 1$  for all cases (within and outside the subcohort),
  - $w = N_{\text{non-cases}}/n_{\text{non-cases}} = \text{inverse of sampling-fraction } f \text{ for selecting a non-case to the subcohort.}$
- ▶ Function `coxph()` with option `weights = w` would provide consistent estimation of  $\beta$  parameters.
- ▶ However, the SEs must be corrected!
- ▶ R solution: Function `cch()` – a wrapper of `coxph()` – in package `survival`, with `method = "LinYing"`.

Nested case-control and case-cohort studies

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## Comparison of NCC and CC designs

- ▶ Statistical efficiency  
Broadly similar in NCC and CC with similar numbers of cases and controls.
- ▶ Statistical modelling and valid inference  
Straightforward for both designs with appropriate software, now widely available for CC, too
- ▶ Analysis of outcome rates on several time scales?  
**NCC:** Only the time scale used in risk set definition can be the time variable  $t$  in the baseline hazard of PH model.  
**CC:** Different choices for the basic time in PH model possible, because subcohort members are not time-matched to cases.

Nested case-control and case-cohort studies

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## Comparison of designs (cont'd)

- ▶ Missing data

**NCC:** With close 1:1 matching, a case-control pair is lost, if either of the two has data missing on key exposure(s).

**CC:** Missingness of few data items is less serious.

- ▶ Quality and comparability of biological measurements

**NCC:** Allows each case and its controls to be matched also for analytic batch, storage time, freeze-thaw cycle, → better comparability.

**CC:** Measurements for subcohort performed at different times than for cases → differential quality & misclassification.

- ▶ Possibility for studying many diseases with same controls

**NCC:** Complicated, but possible if matching is not too refined.

**CC:** Easy, as no subcohort member is “tied” with any case.

Nested case-control and case-cohort studies

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## Conclusion

- ▶ “Case-controlling” is very cost-effective.
- ▶ Case-cohort design is useful especially when several outcomes are of interest, given that the measurements on stored materials remain stable during the study.
- ▶ Nested case-control design is better suited e.g. for studies involving biomarkers that can be influenced by analytic batch, long-term storage, and freeze-thaw cycles.
- ▶ Matching helps in improving efficiency and in reducing bias – but only if properly done.
- ▶ Handy R tools are available for all designs.

Nested case-control and case-cohort studies

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## Some topics on causal inference

Krista Fischer

Institute of Mathematics and Statistics, University of Tartu  
Estonian Genome Center, Institute of Genomics, University of Tartu

Statistical Practice in Epidemiology, Tartu 2019

1/24

Outline   How to define a causal effect?   Causal graphs, confounding and adjustment   Causal models for observational data   Summary

## How to define a causal effect?

## Causal graphs, confounding and adjustment

## Causal models for observational data

## Instrumental variables estimation and Mendelian randomization

## Summary and references

## References

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Outline **How to define a causal effect?** Causal graphs, confounding and adjustment Causal models for observational data Summary

## Statistical associations vs causal effects in epidemiology

Does the exposure (smoking level, obesity, etc) have a causal effect on the outcome (cancer diagnosis, mortality, etc)?

is not the same question as

Is the exposure associated with the outcome?

Conventional statistical analysis will answer the second one, but not necessarily the first.

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Conventional statistical analysis will answer the second one, but not necessarily the first.

## What is a causal effect?

*There is more than just one way to define it.*

A causal effect may be defined:

- ▶ At the **individual level**:  
*Would my cancer risk be different if I were a (non-)smoker?*
- ▶ At the population level:  
*Would the population cancer incidence be different if the prevalence of smoking were different?*
- ▶ At the *exposed subpopulation level*:  
Would the cancer incidence in smokers be different if they were nonsmokers?

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## Causal effects and counterfactuals

- ▶ Defining the causal effect of an observed exposure always involves some **counterfactual** (what-if) thinking.
- ▶ The individual causal effect can be defined as the difference

- Sometimes people (e.g. J. Pearl) use the “do” notation to distinguish counterfactual variables from the observed ones:  $Y(\text{do}(X = 1))$  and  $Y(\text{do}(X = 0))$ .

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## Counterfactual outcomes in different settings

- ▶ Randomized trials: probably the easiest setting to imagine  $Y(X)$  for different  $X$
- ▶ “Actionable” exposures: smoking level, vegetable consumption, ... – potential interventions may alter exposure levels in future.
- ▶ **Non-actionable exposures**: e.g genotypes. It is difficult to ask “*What if I had different genes?*”. Still useful concept to formalize genetic effects (heritability, attributable risk).
- ▶ **Combinations**: With  $X$  – a behavioral intervention level,  $Z$  – smoking level and  $Y$  – a disease outcome, one could formalize the effect of intervention on outcome by using  $Y(X, Z(X))$

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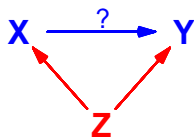
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## Classical/generalized regression estimates vs causal effects?

- ▶ In the presence of confounding, regression analysis provides a biased estimate for the true causal effect
- ▶ To reduce such bias, one needs to collect data on most important confounders and adjust for them
- ▶ However, too much adjustment may actually introduce more biases
- ▶ Causal graphs (Directed Acyclic Graphs, DAGs) may be extremely helpful in identifying the optimal set of adjustment variables

## Adjustment for confounders I

“Classical” confounding: situation where third factors  $Z$  influence both,  $X$  and  $Y$



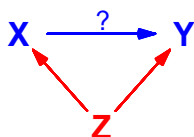
For instance, one can assume:  $X = Z + U$  and  $Y = Z + V$ , where  $U$  and  $V$  are independent of  $Z$ .

$X$  and  $Y$  are independent, conditional on  $Z$ , but marginally dependent.

One should adjust the analysis for  $Z$ , by fitting a regression model for  $Y$  with covariates  $X$  and  $Z$ . There is a causal effect between  $X$  and  $Y$ , if the effect of  $X$  is present in such model.

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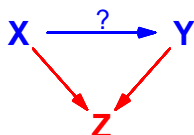
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## Adjustment may sometimes make things worse

Example: the effect of  $X$  and  $Y$  on  $Z$ :



A simple model may hold:  $Z = X + Y + U$ ,

where  $U$  is independent of  $X$  and  $Y$ .

Hence  $Y = Z - X - U$ .

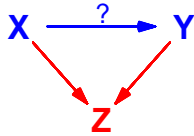
We see the association between  $X$  and  $Y$  only when the “effect” of  $Z$  has been taken into account. But this is not the causal effect of  $X$  on  $Y$ .

One should NOT adjust the analysis for  $Z$ !



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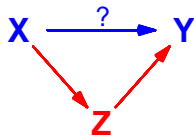
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## More possibilities: mediation

Example: the effect of  $X$  on  $Y$  is (partly) **mediated** by  $Z$ :



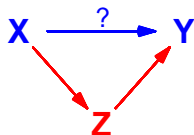
$$Y = X + Z + U,$$

If you are interested in the **total effect** of  $X$  on  $Y$  – don’t adjust  
for  $Z$ !

If you are interested in the **direct effect** of  $X$  on  $Y$  – adjust for  $Z$ .  
(Only if the  $Z$ - $Y$  association is unconfounded)

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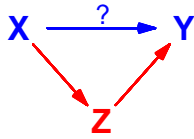
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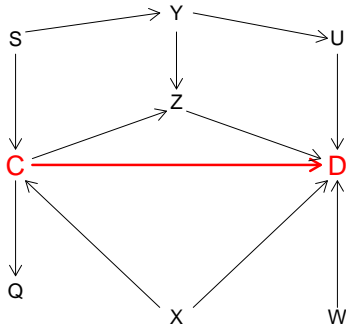


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Actually there might be a complicated system of causal effects:



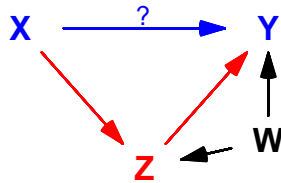
C-smoking; D-cancer

Q, S, U, W, X, Y, Z - other factors that influence cancer risks and/or smoking (genes, social background, nutrition, environment, personality, ...)

To check for confounding,

1. Sketch a causal graph
2. Remove all arrows corresponding to the causal effect of interest (thus, create a graph where the causal null-hypothesis would hold).
3. Remove all nodes (and corresponding edges) except those contained in the exposure ( $C$ ) and outcome ( $D$ ) variables and their (direct or indirect) ancestors.
4. Connect by an undirected edge every pair of nodes that both share a common child and are not already connected by a directed edge.
  - ▶ If now  $C$  and  $D$  are still associated, we say that the  $C - D$  association is confounded
  - ▶ Identify the set of nodes that need to be deleted to separate  $C$  and  $D$  – inferences conditional on these variables give unconfounded estimates of the causal effects.

## Example: mediation with confounding



Follow the algorithm to show that one should adjust the analysis for  $W$ . If  $W$  is an unobserved confounder, no valid causal inference is possible in general. However, the total effect of  $X$  on  $Y$  is estimable.

## “Mendelian randomization” – genes as Instrumental Variables

- ▶ Most of the exposures of interest in chronic disease epidemiology cannot be randomized.
- ▶ Sometimes, however, nature will randomize for us: there is a SNP (Single nucleotide polymorphism, a DNA marker) that affects the exposure of interest, but not directly the outcome.
- ▶ Example: a SNP that is associated with the enzyme involved in alcohol metabolism, genetic lactose intolerance, etc.

However, the crucial assumption that the SNP cannot affect outcome in any other way than throughout the exposure, cannot be tested statistically!

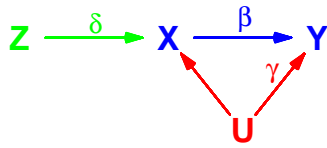
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## General instrumental variables estimation

A causal graph with exposure  $X$ , outcome  $Y$ , confounder  $U$  and an *instrument*  $Z$ :



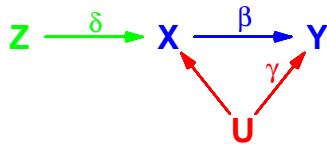
Simple regression will yield a biased estimate of the causal effect of  $X$  on  $Y$ , as the graph implies:

$$Y = \alpha_Y + \beta X + \gamma U + \epsilon, \quad E(\epsilon|X, U) = 0$$

so  $E(Y|X) = \alpha_Y + \beta X + \gamma E(U|X)$ .

Thus the coefficient of  $X$  will also depend on  $\gamma$  and the association between  $X$  and  $U$ .

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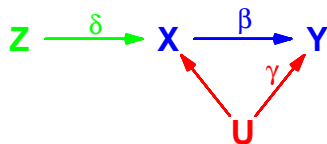
How can  $Z$  help?

If  $E(X|Z) = \alpha_X + \delta Z$ , we get

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As  $\delta$  and  $\beta\delta$  are estimable, also  $\beta$  becomes estimable.

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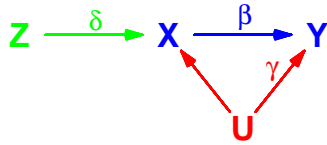
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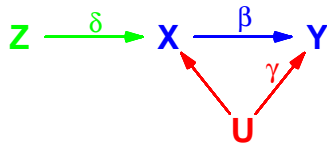
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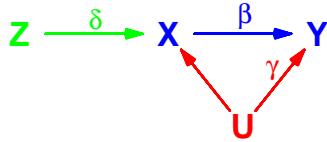
How can Z help?

If  $E(X|Z) = \alpha_X + \delta Z$ , we get

$$E(Y|Z) = \alpha_Y + \beta E(X|Z) + \gamma E(U|Z) = \alpha_Y + \beta(\alpha_X + \delta Z) = \alpha_Y^* + \beta\delta Z.$$

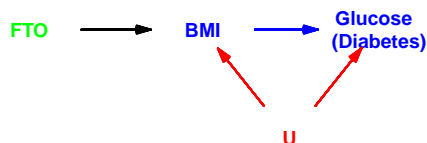
As  $\delta$  and  $\beta\delta$  are estimable, also  $\beta$  becomes estimable.

## General instrumental variables estimation



1. Regress  $X$  on  $Z$ , obtain an estimate  $\hat{\delta}$
2. Regress  $Y$  on  $Z$ , obtain an estimate  $\hat{\delta}\beta$
3. Obtain  $\hat{\beta} = \frac{\hat{\delta}\beta}{\hat{\delta}}$
4. Valid, if  $Z$  is not associated with  $U$  and does not have any effect on  $Y$  (other than mediated by  $X$ )
5. Standard error estimation is more tricky – use for instance `library(sem)`, function `tsls()`.

FTO genotype, BMI and Blood Glucose level (related to Type 2 Diabetes risk; Estonian Biobank, n=3635, aged 45+)



- ▶ Average difference in Blood Glucose level (Glc, mmol/L) per BMI unit is estimated as 0.085 (SE=0.005)
- ▶ Average BMI difference per FTO risk allele is estimated as 0.50 (SE=0.09)
- ▶ Average difference in Glc level per FTO risk allele is estimated as 0.13 (SE=0.04)
- ▶ Instrumental variable estimate of the mean Glc difference per BMI unit is 0.209 (se=0.078)

```
> summary(tsls(Glc~bmi, ~fto,data=fen),digits=2)

2SLS Estimates

Model Formula: Glc ~ bmi

Instruments: ~fto

Residuals:
    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
-6.3700 -1.0100 -0.0943  0.0000  0.8170 13.2000

              Estimate Std. Error t value Pr(>|t|)
(Intercept)   -1.210      2.106    -0.6    0.566
bmi             0.209      0.078     2.7    0.008 **
```

```
> summary(lm(Glc~bmi+fto,data=fen))
Coefficients:
              Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.985     0.106    18.75  <2e-16 ***
bmi          0.088     0.004    23.36  <2e-16 ***
fto          0.049     0.030     1.66   0.097 .
---
For Type 2 Diabetes:
> summary(glm(t2d~bmi+fto,data=fen,family=binomial))
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept) -7.515     0.187   -40.18  <2e-16 ***
bmi          0.185     0.006    31.66  <2e-16 ***
fto          0.095     0.047     2.01   0.044 *
```

A significant FTO effect would not be a proof here (nor does non-significance prove the opposite)! (WHY?)

## Can we test pleiotropy?

A naïve approach would be to fit a linear regression model for  $Y$ , with both  $X$  and  $G$  as covariates.

But in this case we estimate:

$$E(Y|X, G) = \text{const} + \beta_{PI}G + \beta X + \gamma E(U|X, G).$$

It is possible to show that  $U$  is not independent of neither  $X$  nor  $G$  – therefore, the coefficient of  $G$  in the resulting model would be nonzero even if  $\beta_{PI} = 0$ .

Therefore there is no formal test for pleiotropy possible in the case of one genetic instrument – only biological arguments could help to decide, whether assumptions are likelt to be fulfilled

In the case of *multiple genetic instruments* and *meta-analysis*, sometimes the approach of *Egger regression* can be used (Bowden et al, 2015). But even that is not an assumption-free method!

## Summary

- ▶ There is no unique definition of “the causal effect”
- ▶ The validity of any causal effect estimates depends on the validity of the underlying assumptions.
- ▶ Adjustment for other available variables may remove (some) confounding, but it may also create more confounding. **Do not adjust for variables that may themselves be affected by the outcome.**
- ▶ Instrumental variables approaches can be helpful, but beware of assumptions!

## Some references

- ▶ A webpage by Miguel Hernan and Jamie Robins: <http://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/>
- ▶ *An overview of Mendelian randomization*: Sheehan, N., Didelez, V., et al., Mendelian Randomization and Causal Inference in Observational Epidemiology, PLoS Med. 2008 August; 5(8).
- ▶ *A way to correct for pleiotropy bias*: Bowden J, Davey Smith G, Burgess S, Mendelian randomization with invalid instruments. Int J Epidemiol. 2015 Apr;44(2):512-25.
- ▶ ... and how to interpret the findings (warning against overuse): Burgess S., Thompson, S.G., Interpreting findings from Mendelian randomization using the MR-Egger method, Eur J Epidemiol (2017).
- ▶ A lot of ongoing research on Mendelian randomization ... (see recent papers by Jack Bowden, Stephen Burgess and others on methodological advances, follow e.g. @MR\_lit on Twitter for case studies) and causal inference in general

# Multistate models

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August 2019

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From /home/bendix/teach/SPE/git/SPE/lectures/multistate/multistate.tex

Tuesday 27<sup>th</sup> August, 2019, 10:33

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## Multistate models

**Bendix Carstensen, Martyn Plummer**

Multistate models

SPE, Tartu, Estonia,

August 2019

<http://BendixCarstensen.com/SPE>

ms-Markov

## Common assumptions in survival analysis

1. Subjects are **either** “healthy” **or** “diseased”, with no intermediate state.
2. The disease is **irreversible**, or requires intervention to be cured.
3. The time of disease incidence is known **exactly**.
4. The disease is **accurately** diagnosed.

These assumptions are true for **death** and many **chronic diseases**.



## A model for cervical cancer

Invasive squamous cell cancer of the cervix is preceded by cervical intraepithelial neoplasia (CIN)



- ▶ Aim of the modeling the **transition rates** between **states**, is to be able predict how population moves between states:
- ▶ **state** occupancy probabilities
- ▶ visit probability
- ▶ length of stay (sojourn time)

Multistate models (ms-Markov)

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## Markov models for multistate diseases

Generalization of Poisson regression to multiple disease states:

- ▶ Transition rates between states depends **only** on current state (and possibly time since start) — the **Markov** property
- ▶ (time-fixed) covariates may influence transition rates
- ▶ the formal Markov property is **very** restrictive
- ▶ **semi**-Markov: rates depend on time since entry to current state
- ▶ In the clinical literature, the term “Markov model” is often used about any type of multistate model
- ▶ ... and the Markov property is handy in probability theory

Multistate models (ms-Markov)

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## Components of a multistate (Markov) model

- ▶ Define the (disease) states
- ▶ Define which transitions between states that occur
- ▶ Select covariates influencing transition rates (may be different between transitions)
- ▶ Constrain some covariate effects to be the same, or zero.
- ▶ Not a trivial task — do we want e.g.
  - ▶ cause of death
  - ▶ disease status at death

Multistate models (ms-Markov)

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## Components of multistate data

Times should be recorded as **dates**

- ▶ birth date
- ▶ entry date
- ▶ entry **state**
- ▶ exit date
- ▶ death date
- ▶ state entry dates — for all states
- ▶ ... some states may be revisited

From this each person's trajectory through states can be constructed

Multistate models (ms-Markov)

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## Likelihood for multistate model

- ▶ The likelihood of the observed data (sojourn times and transitions) depend on the (models for) the transition rates.
- ▶ Assume transition rates are constant in small time intervals
- ▶  $\Rightarrow$  each interval contributes terms to the log-likelihood:
  - ▶ one for each person ( $p$ ) at risk in state  $s$  in the interval
  - ▶ ... for each possible transition ( $s \rightarrow v$ )
  - ▶ each term is a Poisson log-likelihood contribution:

$$d_{psv} \log(\lambda_{psv}) - \lambda_{psv} y_{ps}, \quad \text{where:}$$

- $\lambda_{psv}$  rate for person  $p$  in state  $s$  going to state  $v$
  - $d_{psv}$  did person  $p$  in state  $s$  go to state  $v$  at end of interval
  - $y_{ps}$  how long did person  $p$  spend in state  $s$  (how long is the interval)
- ▶ Total log-lik is sum of terms over persons and transitions

Multistate models (ms-Markov)

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## Practical multistate modeling

- ▶ Total log-lik is sum of terms over persons ( $p$ ) and transitions ( $s \rightarrow v$ )
- ▶ — components **not** independent, but the total likelihood is a product; hence of the same form as the likelihood of independent Poisson variates
- ▶ practical analysis is just analysis of each transition rate separately
- ▶ as long as no two rates **out** of the **same** state are modeled we can use subsets of Lexis objects

Multistate models (ms-Markov)

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# Multistate models with Lexis

Bendix Carstensen

Multistate models

SPE, Tartu, Estonia,

August 2019

<http://BendixCarstensen.com/SPE>

ms-Lexis

## Example: Renal failure data from Steno

Hovind P, Tarnow L, Rossing P, Carstensen B, and Parving H-H: Improved survival in patients obtaining remission of nephrotic range albuminuria in diabetic nephropathy. *Kidney Int.*, 66(3):1180–1186, 2004.

- ▶ 96 patients entering at nephrotic range albuminuria (NRA), i.e.  $U\text{-alb} > 300\text{mg/day}$ .
- ▶ Is remission from this condition (i.e return to  $U\text{-alb} < 300\text{mg/day}$ ) predictive of the prognosis?
- ▶ Endpoint of interest: Death or end stage renal disease (ESRD), i.e. dialysis or kidney transplant.

Multistate models with Lexis (ms-Lexis)

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	Total	Remission	
		Yes	No
No. patients	125	32	93
No. events	77	8	69
Follow-up time (years)	1084.7	259.9	824.8
Cox-model:			
Timescale:	Time since nephrotic range albuminuria (NRA)		
Entry:	2.5 years of GFR-measurements after NRA		
Outcome:	ESRD or Death		
Estimates:	RR	95% c.i.	p
Fixed covariates:			
Sex (F vs. M):	0.92	(0.53,1.57)	0.740
Age at NRA (per 10 years):	1.42	(1.08,1.87)	0.011
Time-dependent covariate:			
Obtained remission:	0.28	(0.13,0.59)	0.001

Multistate models with Lexis (ms-Lexis)

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## Features of the analysis

- ▶ Remission is included as a time-dependent variable.
- ▶ Age at entry is included as a fixed variable.

```
renal[1:5,]
id    dob    doe    dor    dox event
17 1967.944 1996.013    NA 1997.094    2
26 1959.306 1989.535 1989.814 1996.136    1
27 1962.014 1987.846    NA 1993.239    3
33 1950.747 1995.243 1995.717 2003.993    0
42 1961.296 1987.884 1996.650 2003.955    0
```

Note patient 26, 33 and 42 obtain remission.

Multistate models with Lexis (ms-Lexis)

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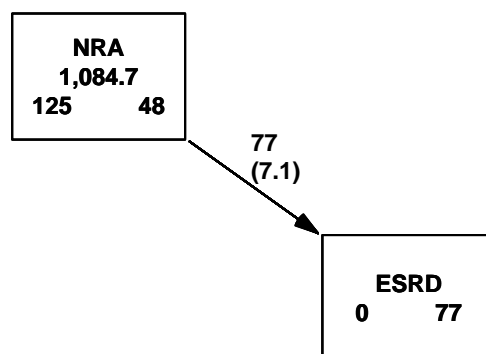
```
> Lr <- Lexis( entry = list( per=doe,
+                           age=doe-dob,
+                           tfi=0 ),
+             exit = list( per=dox ),
+             exit.status = event>0,
+             states = c("NRA","ESRD"),
+             data = renal )
> summary( Lr )

Transitions:
  To
From  NRA  ESRD  Records:  Events:  Risk time:  Persons:
  NRA   48   77      125      77    1084.67      125
```

Multistate models with Lexis (ms-Lexis)

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```
> boxes( Lr, boxpos=list(x=c(25,75),
+                          y=c(75,25)),
+        scale.R=100, show.BE=TRUE )
```



Multistate models with Lexis (ms-Lexis)

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## Cutting follow-up at remission: cutLexis

```
> Lc <- cutLexis( Lr, cut=Lr$dor,
+                 timescale="per",
+                 new.state="Rem",
+                 precursor.states="NRA" )
> summary( Lc )
```

Transitions:

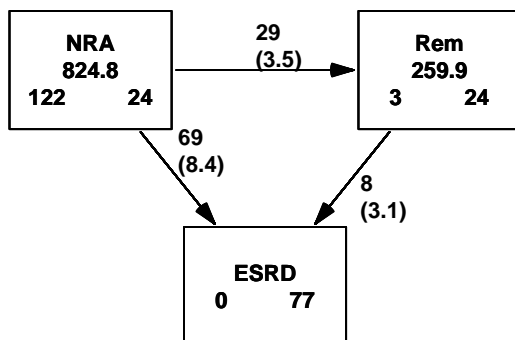
From	To	NRA	Rem	ESRD	Records:	Events:	Risk time:	Persons:
NRA		24	29	69	122	98	824.77	122
Rem		0	24	8	32	8	259.90	32
Sum		24	53	77	154	106	1084.67	125

Multistate models with Lexis (ms-Lexis)

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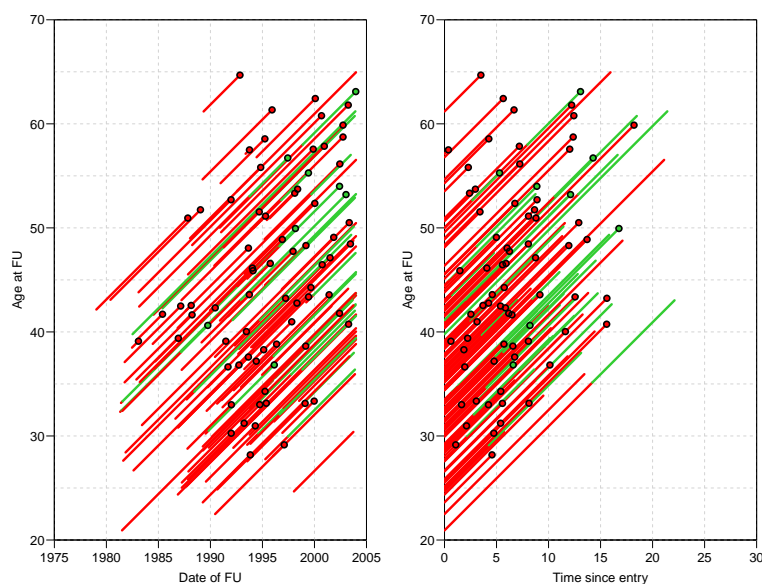
## Showing states and FU: boxes.Lexis

```
> boxes( Lc, boxpos=list(x=c(15,85,50),
+                         y=c(85,85,20)),
+        scale.R=100, show.BE=TRUE )
```



Multistate models with Lexis (ms-Lexis)

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Multistate models with Lexis (ms-Lexis)

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## Splitting states: cutLexis

```
> Lc <- cutLexis( Lr, cut=Lr$dor,
+               timescale="per",
+               new.state="Rem",
+               precursor.states="NRA",
+               split.states=TRUE )
> summary( Lc )
```

Transitions:

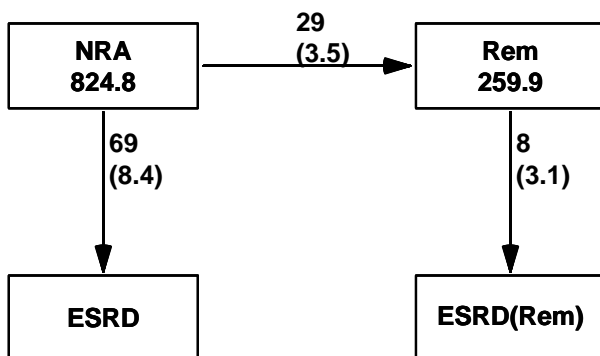
	From	To	NRA	Rem	ESRD	ESRD (Rem)	Records:	Events:	Risk time:	Persons:
NRA	24	29	69			0	122	98	824.77	122
Rem	0	24	0			8	32	8	259.90	32
Sum	24	53	69			8	154	106	1084.67	125

Multistate models with Lexis (ms-Lexis)

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## Showing states and FU: boxes.Lexis

```
> boxes( Lc, boxpos=list(x=c(15,85,15,85),
+                          y=c(85,85,20,20)), scale.R=100 )
```



Multistate models with Lexis (ms-Lexis)

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## Likelihood for a general MS-model

- ▶ Product of likelihoods for each transition  
— each one as for a survival model
- ▶ **Risk time** is the risk time in the “From” state
- ▶ **Events** are transitions to the “To” state
- ▶ All other transitions out of “From” are treated as **censorings**
- ▶ Possible to fit models separately for each transition

Multistate models with Lexis (ms-Lexis)

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# Prediction in multistate models: simLexis and renal failure

Bendix Carstensen

Multistate models

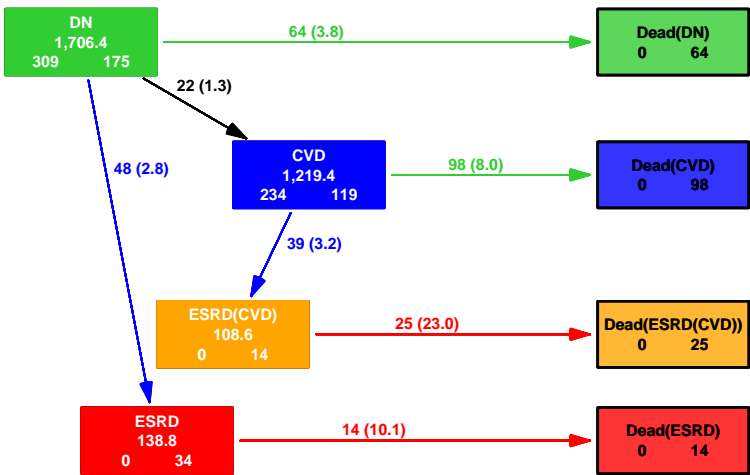
SPE, Tartu, Estonia,

August 2019

<http://BendixCarstensen.com/SPE>

simRenal

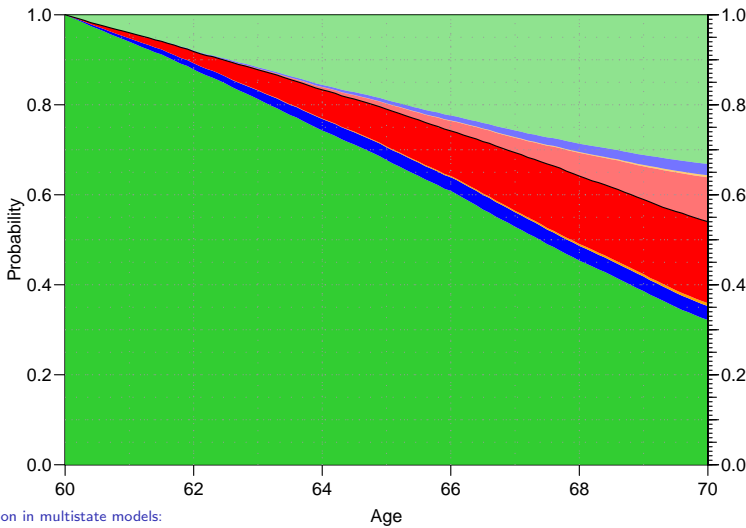
## A more complicated multistate model



Prediction in multistate models:  
simLexis and renal failure (simRenal)

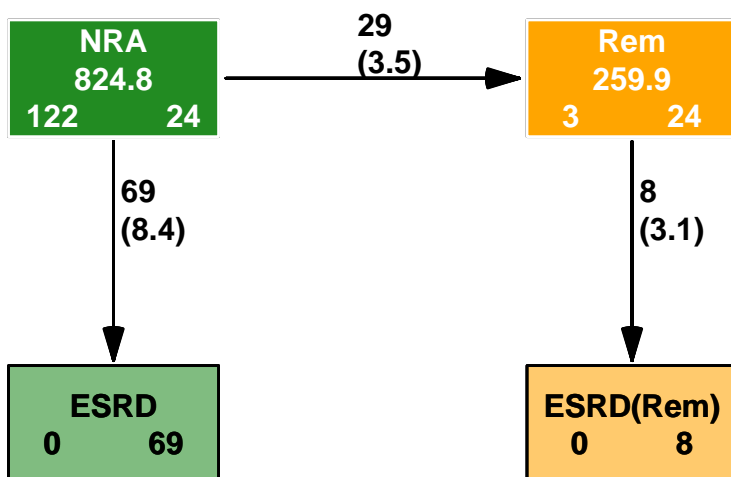
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## A more complicated multistate model



Prediction in multistate models:  
simLexis and renal failure (simRenal)

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Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## Modeling in a multistate model

Each transition modeled by a model for rates (Cox-model, Poisson-model for split data, glm or gam):

```

> sLc <- splitLexis( Lc, "tfi", breaks=seq(0,30,1/12) )
> # Rem-rate
> mr <- gam( cbind(lex.Xst=="Rem",lex.dur)
+           ~ s( tfi, k=10 ) + sex,
+           family = poisreg,
+           data = subset( sLc, lex.Cst=="NRA" ) )
> # ESRD-rates
> mx <- gam( cbind( lex.Xst %in% c("ESRD","ESRD(Rem)"), lex.dur )
+           ~ s(tfi,k=10) + sex + I((doe-dob-40)/10) + I(lex.Cst=="Rem"),
+           family = poisreg,
+           data = subset(sLc, lex.Cst %in% c("NRA","Rem")) )
  
```

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## ...using the Lexis properties

```

> # Rem-rate
> mr <- gam.Lexis( sLc, from="NRA", to="Rem",
+               formula = ~ s( tfi, k=10 ) + sex )

mgcv::gam Poisson analysis of Lexis object sLc with log link:
Rates for the transition: NRA->Rem

> # ESRD-rates
> mx <- gam.Lexis( sLc, formula = ~ s(tfi,k=10) + sex +
+               I((doe-dob-40)/10) + I(lex.Cst=="Rem") )

mgcv::gam Poisson analysis of Lexis object sLc with log link:
Rates for transitions: NRA->ESRD, Rem->ESRD(Rem)
  
```

Default is to model all transitions

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## State probabilities

How do we get from rates (Poisson-models) to probabilities:

### 1 Analytic calculations:

- ▶ immensely complicated formulae
- ▶ computationally fast (once implemented)
- ▶ difficult to generalize

### 2 Simulation of persons' histories

- ▶ conceptually simple
- ▶ computationally not quite simple
- ▶ easy to generalize
- ▶ hard to get confidence intervals (bootstrap)

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## Simulation of a survival time

- ▶ For a rate function  $\lambda(t)$ ,  $\Lambda(t) = \int_0^t \lambda(s) ds$ :

$$S(t) = \exp(-\Lambda(t))$$

- ▶ Simulate a survival probability  $u \in [0, 1]$ :

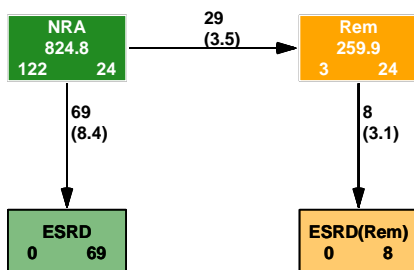
$$u = S(t) \Leftrightarrow \Lambda(t) = -\log(u)$$

- ▶ Knowledge of  $\Lambda(t)$  makes it easy to find a survival time — essentially just linear interpolation.

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## Simulation in a multistate model

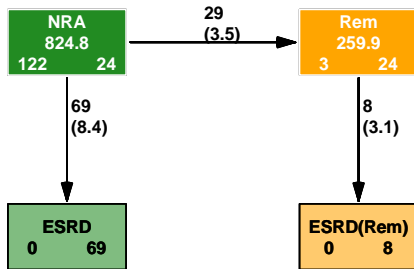


- ▶ Simulate a “survival time” for each transition **out** of a state.
- ▶ The smallest of these is the transition time.
- ▶ Choose the corresponding transition type as transition.

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## Transition objects are glm/gam



```
> Tr <- list( "NRA" = list( "ESRD"      = mx,
+                           "Rem"       = mr ),
+            "Rem" = list( "ESRD(Rem)" = mx ) )
```

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## simLexis

Input required:

- ▶ A Lexis object representing the initial state of the persons to be simulated.  
(lex.dur and lex.Xst will be ignored.)
- ▶ A transition object with the estimated Poisson models collected in a list of lists.

Output produced:

- ▶ A Lexis object with simulated event histories for many persons
- ▶ Use nState to count how many persons in each state at different times

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## Using simLexis I

Put one record a new Lexis object (init, say). representing a person with the desired covariates.

Must have same structure as the one used for estimation — time scales must be initiated even if not used in models

```
> init <- sLc[NULL, c(timeScales(sLc), "lex.Cst")]
> init[1, "per"] <- 1994
> init[1, "age"] <- 40
> init[1, "tfi"] <- 0
> init[1, "lex.Cst"] <- "NRA"
> init[1, "sex"] <- "M"
> init[1, "dob"] <- 1954
> init[1, "doe"] <- 1994
> init
```

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## Using simLexis II

```
per age tfi lex.Cst sex dob doe
1 1994 40 0 NRA M 1954 1994

> system.time(
+ sim1 <- simLexis( Tr, init, N=10000 ) )

user system elapsed
49.608 52.279 36.550

> summary(sim1)

Transitions:
To
From NRA Rem ESRD ESRD(Rem) Records: Events: Risk time: Persons:
NRA 314 1870 7816 0 10000 9686 74864.10 10000
Rem 0 940 0 930 1870 930 20593.77 1870
Sum 314 2810 7816 930 11870 10616 95457.87 10000
```

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## Using a simulated Lexis object — pState I

```
> NN <- nState( sim1, at = seq(0,15,0.1),
+               from = 0,
+               time.scale = "tfi" )
> head( NN )

State
when   NRA   Rem   ESRD ESRD(Rem)
0      10000  0      0      0
0.1    9940  39     21      0
0.2    9891  60     49      0
0.3    9834  83     83      0
0.4    9793  100    107     0
0.5    9731  134    135     0

> nw1 <- pState( NN, perm = c(1,2,4,3) )
> head( nw1, 3 )
```

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## Using a simulated Lexis object — pState II

```
State
when   NRA   Rem   ESRD(Rem) ESRD
0      1.0000 1.0000 1.0000 1
0.1    0.9940 0.9979 0.9979 1
0.2    0.9891 0.9951 0.9951 1

> tail( nw1, 3 )

State
when   NRA   Rem   ESRD(Rem) ESRD
14.8  0.0996 0.2200 0.2802 1
14.9  0.0971 0.2171 0.2779 1
15    0.0953 0.2151 0.2763 1

> par( mar=c(3,3,0.1,0.1), mgp=c(3,1,0)/1.6, las=1 )
> plot( nw1, col=clr[c(2,1,4,3)] )
> lines( as.numeric(rownames(nw1)), nw1[,2] )
```

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## Using a simulated Lexis object — pState III

```
> nw2 <- pState( NN, perm = c(4,2,1,3) )
> head( nw2, 3 )

      State
when  ESRD(Rem)    Rem    NRA ESRD
  0         0 0.0000 1.0000    1
  0.1       0 0.0039 0.9979    1
  0.2       0 0.0060 0.9951    1

> tail( nw2, 3 )

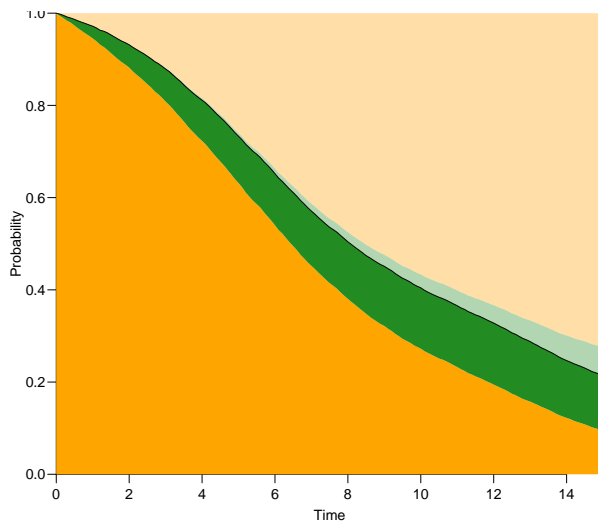
      State
when  ESRD(Rem)    Rem    NRA ESRD
 14.8    0.0602 0.1806 0.2802    1
 14.9    0.0608 0.1808 0.2779    1
 15      0.0612 0.1810 0.2763    1

> par( mar=c(3,3,0.1,0.1), mgp=c(3,1,0)/1.6, las=1 )
> plot( nw2, col=clr[c(4,1,2,3)] )
```

Prediction in multistate models:  
simLexis and renal failure (simRenal)

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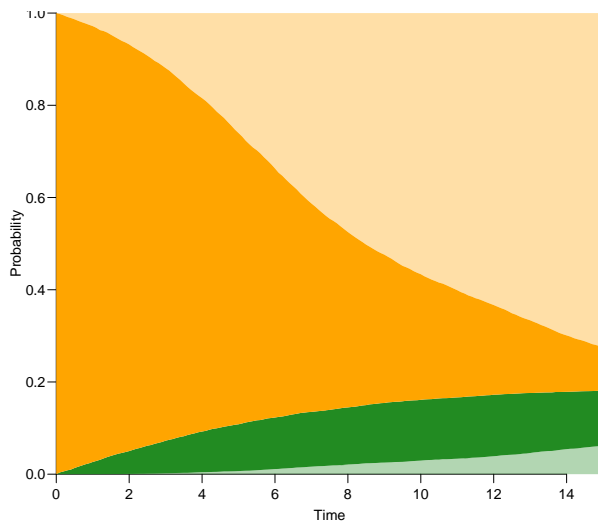
## Simulated probabilities



Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## Simulated probabilities



Prediction in multistate models:  
simLexis and renal failure (simRenal)

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## How many persons should you simulate?

- ▶ All probabilities have the same denominator — the initial number of persons in the simulation,  $N$ , say.
- ▶ Thus, any probability will be of the form  $p = x/N$
- ▶ For small probabilities we have that:

$$\text{s.e.}(\log(\hat{p})) = (1 - p)/\sqrt{Np(1 - p)}$$

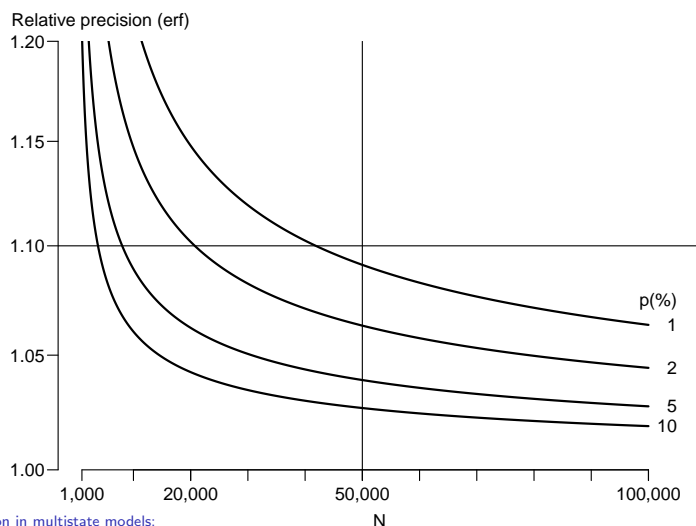
- ▶ So c.i. of the form  $p \div \text{erf}$  where:

$$\text{erf} = \exp(1.96 \times (1 - p)/\sqrt{Np(1 - p)})$$

Prediction in multistate models:  
[simLexis](#) and renal failure ([simRenal](#))

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## Precision of simulated probabilities



Prediction in multistate models:  
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## Multistate model overview

- ▶ Clarify what the relevant states are
- ▶ Allows proper estimation of transition rates
- ▶ — and relationships between them
- ▶ Separate model for each transition (arrow)
- ▶ The usual survival methodology to compute probabilities breaks down
- ▶ Simulation allows estimation of cumulative probabilities:
  - ▶ Estimate transition rates (as usual)
  - ▶ Simulate probabilities (**not** as usual)

Prediction in multistate models:  
[simLexis](#) and renal failure ([simRenal](#))

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