History and Ecology of R

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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`

The "Blue Book" and the "White Book"

Key features of S version 3 outlined in two books:

- Becker, Chambers and Wilks, *The New S Language: A Programming Environment for Statistical Analysis and Graphics* (1988)
  - Functions and objects
- Chambers and Hastie (Eds), *Statistical Models in S* (1992)
  - Data frames, formulae

These books were later used as a prototype for R.

Programming with Data

> *"We wanted users to be able to begin in an interactive environment, where they did not consciously think of themselves as programming. Then as their needs became clearer and their sophistication increased, they should be able to slide gradually into programming." – John Chambers, Stages in the Evolution of S*

This philosophy was later articulated explicitly in *Programming With Data* (Chambers, 1998) as a kind of mission statement for S

> *To turn ideas into software, quickly and faithfully*

The "Green Book"

Key features of S version 4 were outlined in Chambers, *Programming with Data* (1998).

- S as a programming language
- Introduced formal classes and methods, which were later introduced into R by John Chambers himself.

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, ...

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.

History

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

The Dawn of R

- Ross Ihaka and Robert Gentlemen at the University of Auckland
- An experimental statistical environment
- Scheme interpreter with S-like syntax
  - Replaced scalar type with vector-based types of S
  - Added lazy evaluation of function arguments
- Announced to *s-news* mailing list in August 1993.

A free software project

- June 1995. Martin Maechler (ETH, Zurich) persuades Ross and Robert to release R under GNU Public License (GPL)
- March 1996. Mailing list *r-testers* mailing list
  - Later split into three *r-announce*, *r-help*, and *r-devel*.
- Mid 1997. Creation of *core team* with access to central repository (CVS)
  - Doug Bates, Peter Dalgaard, Robert Gentleman, Kurt Hornik, Ross Ihaka, Friedrich Leisch, Thomas Lumley, Martin Maechler, Paul Murrell, Heiner Schwarte, Luke Tierney
- 1997. Adopted by the GNU Project as "GNU S".

The draw of S

> *"Early on, the decision was made to use S-like syntax. Once that decision was made, the move toward being more and more like S has been irresistible"*
> *– Ross Ihaka, R: Past and Future History (Interface '98)*

R 1.0.0, a complete and stable implementation of S version 3, was released in 2000.

A Souvenir

Packages

- Comprehensive R Archive Network (CRAN) started in 1997
  - Quality assurance tools built into R
  - Increasingly demanding with each new R release
- Recommended packages distributed with R
  - Third-party packages included with R distribution
  - Provide more complete functionality for the R environment
  - Starting with release 1.3.0 (completely integrated in 1.6.0)

Growth of CRAN

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.

Community

- 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

Much important R infrastructure is now in package space

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The tidyverse

- Many of the popular packages on CRAN were written by Hadley Wickham and a team of collaborators working for the company R Studio.
- These packages became known as the "hadleyverse" until Hadley himself rebranded them the "tidyverse" (`www.tidyverse.org`).
- All packages in the tidyverse have a common design philosophy and work together. Common features are:
  - Non-standard evaluation rules for function calls.
  - Use of the pipe operator `%>%` to pass data transparently from one function call to another.
- The CRAN meta-package `tidyverse` installs all of these packages.

Commercial R

Several commercial organizations provide commercial versions of R including support, consulting, ...

- Revolution Computing, later Revolution Analytics (2007–2014), then purchased by Microsoft.
- RStudio (2010–)
- Mango Solutions (2002–)

Validation and Reliability

- *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.

Forks and Clones 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.

The R Foundation for Statistical Computing

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)

The R Consortium

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

The Future

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

Trends

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)

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()`

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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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
```


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"
```


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

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`.

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
```


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`.

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 works 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()
```


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)

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)

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)]
```


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)`;

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
```

Function calls

Round brackets ( ) are used for function calls!

Lots of things you do with R involve calling functions (you have seen that already!).
For instance

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

The important parts of this are

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

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Function arguments

Examples:

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

Items which may appear as arguments:

- 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

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Example

From R-help (`help(t.test)`):

```
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.)

The following lines of code are equivalent:

```
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!
```

Order does not matter for named arguments!
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!

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

Some simple plots:

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

More on factors: the `cut` Function

- The `cut` function converts a numerical variable into groups (a factor variable) according to a set of break points
- The intervals are left-open, right-closed by default (`right=FALSE` changes that)
- ...and that the lowest endpoint is *not* included by default (set `include.lowest=TRUE` if it bothers you)

Example

```
> age <- c(35,20,21,50,46,23,30)
> agegr<-cut(age, c(20,30,40,50))
> table(agegr)
agegr      # the 20-year old is not included!
(20,30] (30,40] (40,50]
      3       1       2
> agegr<-cut(age, c(20,30,40,50),right=FALSE)
> table(agegr)
agegr    # the 50-year old is not included!
[20,30) [30,40) [40,50)
      3       2       1
> agegr<-cut(age, c(20,30,40,50),
+                          include.lowest=TRUE)
> table(agegr)
agegr
[20,30] (30,40] (40,50]
4       1       2
```


Working with Dates

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

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

- You can calculate differences between `Date` objects. The result is an object of class `"difftime"`. To get the number of days between two dates, use

```
> as.numeric(as.Date("2017-6-1")-
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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 Resarch on Cancer

August 2019 - Tartu

Epidemiological study workflow

Data manipulation tools

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

Tidyverse (from 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 **verbes** 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)

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.

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).

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).

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 e**X**it, end of follow-up.

- Follow-up time (years) computed as:

  `y = (dox - doe)/365.25`

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?

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 $\{(y_i, \delta_i); i = 1, ..., n\}$.
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 $D - \lambda Y = 0$

$\rightarrow$ **maximum likelihood estimator** (MLE) of λ:

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

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 tratment 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)

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

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}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 e**X**it, end of follow-up.

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

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:
$(1.49/1.105, 1.49 \times 1.105) = (1.35, 1.64)$.

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
```


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
```

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
```


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
```


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
```

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
```


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

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

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
```

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% $\frac{p}{1-p} \not\approx p$)

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

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

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.

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

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
```

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
```


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(inclusion in study | control) = s_{ctr}
P(inclusion in study | case) = s_{case}
- Model for observed case-control data:

$$\ln[\text{odds (case | incl.) }] = \ln\left[\frac{p}{1-p}\right] + \ln\left[\frac{s_{\text{cas}}}{s_{\text{ctr}}}\right]$$

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

Logistic regression in case-control studies

Analysis of $P(case|inclusion)$ — *i.e.* binary observations:

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

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

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

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**.

Linear and generalized linear models

Saturday 24 August, 2019

Esa Läärä

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.

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.

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))
```


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)" ) )
```


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**?

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)]` – $\widehat{\beta}_j$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

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`".

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'))
```

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?

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`

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.

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`*?*

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`.

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 β_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.

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 μ_{jk} $(j = 1, 2, 3; k = 1, 2)$:

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

Two factors with interaction

- Effect of Z differs at different levels of X:

		$Z = 1$	$Z = 2$
	1	$\mu_{11} = \alpha$	$\mu_{12} = \alpha + \gamma_2$
X	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`.

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)]
```

$\rightarrow$ No need to specify contrasts in model formula!

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_is,
  - **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.

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 $\widehat{s}(X; \beta)$ & its CI

Mean `bweigth` 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.

Penalized spline model with cross-validation

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

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

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.lin()`, `fitted()`, `predict()`, ...
- Model diagnostics:
  `resid()`, `plot.lm()`, ...

Everything You Ever Wanted to Know about Splines...

Martyn Plummer

University of Warwick

August 2019

Overview

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.

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Rinaldi et al, JNCI. 2014 Jun;106(6):dju097

Rinaldi et al, JNCI. 2014 Jun;106(6):dju097

Statisticians against categorization

- Greenland S (1995) Avoiding power loss associated with categorization and ordinal scores in dose-response and trend analysis, Epidemiology, **6**, 450–454.
- Senn S (2005) Dichotomania: an obsessive compulsive disorder that is badly affecting the quality of analysis of pharmaceutical trials.
- Bennette C, and Vickers A, (2012), Against quantiles: categorization of continuous variables in epidemiologic research, and its discontents. BMC Medical Research Methodology 12:21

Epidemiologists against categorization

Rose, G. (1992) The Strategy of Preventive Medicine

- Many diseases are not discrete. Instead there is an underlying continuum of increasing severity (e.g. hypertension).
- In medicine, we tend to conflate a clinical action (treat vs. do not treat) with the presence/absence of disease.
- Disease prevention efforts are best targeted at shifting the distribution of risk for the whole population instead of trying to identify and target a "high risk" group.

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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

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

Why linear interpolation?

Out of all possible curves that go through the observed points, linear interpolation is the one that minimizes the penalty function

$$\int \left(\frac{\partial f}{\partial x}\right)^2 dx$$

What does the penalty mean?

- The contribution to the penalty at each point depends on the steepness of the curve (represented by a colour gradient)
- Any deviation from a straight line between the two fixed points will incur a higher penalty overall.

Extrapolation

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

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

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Why does linear interpolation break down?

- The penalty function

$$\int \left(\frac{\partial f}{\partial x}\right)^2 dx$$

  penalizes the steepness of the curve
- Minimizing the penalty function gives us gives us the "flattest" curve that goes through the points.
  - In between two observations the flattest curve is a straight line.
  - Outside the range of the observations the flattest curve is completely flat.

A roughness penalty

- If we want a fitted curve that extrapolates a linear trend then we want to minimize the curvature.

$$\int \left(\frac{\partial^2 f}{\partial x^2}\right)^2 dx$$

- Like the first penalty function but uses the second derivative of f (i.e. the curvature).
- This is a roughness penalty.

A roughness penalty

- If we want a fitted curve that extrapolates a linear trend then we want to minimize the curvature.

$$\int \left(\frac{\partial^2 f}{\partial x^2} \right)^2 dx$$

- Like the first penalty function but uses the second derivative of f (i.e. the curvature).
- This is a roughness penalty.

What does the roughness penalty mean?

- The contribution to the penalty at each point depends on the curvature (represented by a colour gradient)
- A straight line has no curvature, hence zero penalty.
- Sharp changes in the slope are heavily penalized.

An interpolating cubic spline

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

An interpolating cubic spline

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

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 $\partial^2 f/\partial x^2$

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Brownian motion

- In 1827, botanist Robert Brown observed particles under the microscope moving randomly
- Theoretical explanation by Einstein (1905) in terms of water molecules
- Verified by Perrin (1908). Nobel prize in physics 1927.

Evolution of 1-dimensional Brownian motion with time

- In mathematics a Brownian motion is a stochastic process that randomly goes up or down at any time point
- Also called a Wiener process after American mathematician Norbert Wiener.
- A Brownian motion is fractal – it looks the same if you zoom in and rescale

A partially observed Brownian motion

- Suppose we observe a Brownian motion at three points
- Grey lines show a sample of possible paths through the points
- The black line shows the average over all paths

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A partially observed Brownian motion

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Statistical model for linear interpolation

- Suppose the curve f is generated by the underlying model

$$f(x) = \alpha + \sigma W(x)$$

  where W (for Wiener process) is a Brownian motion
- Then given points $(x_1, f(x_1)) \ldots (x_n, f(x_n))$ the *expected value* of f is the curve we get from linear interpolation.

Integrated Brownian motion

- The value of an integrated Brownian motion is the area under the curve (AUC) of a Brownian motion up to that point.
- AUC goes down when the Brownian motion takes a negative value.

Integrated Brownian motion with drift

Add a mean parameter and a linear trend (drift) to the integrated Brownian motion:

$$f(x) = \alpha + \beta x + \sigma \int_0^x W(z)dz$$

This more complex model is capable of modelling smooth curves.

A partially observed integrated Brownian motion with drift

- Grey lines show a sample of possible paths through the points
- The black line shows the average over all paths

Zoom on the expected value

- The expected value is a cubic spline.
- Extrapolation beyond the boundary of the points is linear (natural spline).

The smoothness paradox

- A cubic natural spline is the smoothest curve that goes through a set of points.
- But the underlying random process $f(x)$ is nowhere smooth.
- $f(x)$ is constantly changing its slope based on the value of the underlying Brownian motion.

The knot paradox

- There are no knots in the underlying model for a cubic natural spline.
- Knots are a result of the observation process.

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Dose response with error

In practice we never know the dose response curve exactly at any point but always measure with error. A spline model is then a compromise between

- Model fit
- Smoothness of the spline

Dose response with error

In practice we never know the dose response curve exactly at any point but always measure with error. A spline model is then a compromise between

- Model fit
- Smoothness of the spline

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 λ determines compromise between model fit (small λ) and smoothness (large λ).

How to choose the tuning parameter λ

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.

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Spline models done badly

- Choose number and placement of knots
- Create a spline bases
- Use spline basis as the design matrix in a generalized linear model.

- Without penalization, model will underfit (too few knots) or overfit (too many knots)
- Placement of knots may create artefacts in the dose-response relationship

Spline models done well

- A knot for every observed value (remember: knots are a product of the observation process).
- Use penalization: find the right compromise between model fit and model complexity.

- In practice we can get a good approximation to this "ideal" model with fewer knots.
- This assumption should be tested

Spline models in R

- Do not use the splines package.
- Use the `gam` function from the mgcv package to fit your spline models.
- The `gam` function chooses number and placement of knots for you and estimates the size of the tuning parameter λ automatically.
- You can use the `gam.check` function to see if you have enough knots. Also re-fit the model explicitly setting a larger number of knots (e.g. double) to see if the fit changes.

Penalized spline

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

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Unpenalized spline

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

Unpenalized spline

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

Conclusions

- Epidemiologists like to turn continuous variables into categories.
- Statisticians do not like categorization because it loses information.
- Splines are a flexible class of models that avoid categorization but also avoid making strong assumptions about the shape of a dose-response relationship.
- Penalized regression splines are based on compromise between goodness-of-fit and smoothness.
- Most of the decisions in fitting a penalized regression spline can be made for you
  - Degree of smoothing
  - Number of knots
  - Placement of knots

More Advanced Graphics in R

Martyn Plummer

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SPE 2019, Tartu

Outline

Overview of graphics systems

Device handling

Base graphics

Lattice graphics

Grid graphics

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.

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

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`)

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.

Approach to Customization

- Start with default plots
- Modify parameters (using `par()` settings or plotting arguments)
- Add more graphics elements. Notice that there are graphics parameters that turn things *off*, e.g. `plot(x, y, xaxt="n")` so that you can add completely customized axes with the `axis` function.
- Put all your plotting commands in a script or inside a function so you can start again

Demo 1

```
library(ISwR)
par(mfrow=c(2,2))
matplot(intake)
matplot(t(intake))
matplot(t(intake),type="b")
matplot(t(intake),type="b",pch=1:11,col="black",
        lty="solid", xaxt="n")
axis(1,at=1:2,labels=names(intake))
```


Margins

- R sometimes seems to leave too much empty space around plots (especially in multi-frame layouts).
- There is a good reason for it: You might want to put something there (titles, axes).
- This is controlled by the `mar` parameter. By default, it is `c(5,4,4,2)+0.1`
  - The units are *lines of text*, so depend on the setting of `pointsize` and `cex`
  - The sides are indexed in clockwise order, starting at the bottom (1=bottom, 2=left, 3=top, 4=right)
- The `mtext` function is designed to write in the margins of the plot
- There is also an *outer margin* settable via the `oma` parameter. Useful for adding overall titles etc. to multiframe plots

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*

Panels

- Plotting functions in `lattice` consistently use a formula interface, e.g `y~x` to plot *y* against *x*
- The formula allows conditioning variables, e.g. `y~x|g1*g2*...`
- Conditioning variables create an array of *panels*,
  - One panel for each value of the conditioning variables
  - Continuous conditioning variables are divided into *shingles* (slightly overlapping ranges, named after the roof covering)
  - All panels have the same scales on the *x* and *y* axes.

Ozone Concentration by Solar Radiation

```
xyplot(log(Ozone)~Solar.R, data=airquality)
```

Conditioned on Temperature

```
xyplot(log(Ozone)~Solar.R | equal.count(Temp),
data=airquality)
```

Coloured by Month

```
xyplot(log(Ozone)~Solar.R | equal.count(Temp),
group=Month, data=airquality)
```

Customizing Panels

- What goes inside each panel of a Lattice plot is controlled by a *panel function*
- There are many standard functions: `panel.xyplot`, `panel.lmline`, etc.
- You can write your own panel functions, most often by combining standard ones

```
mypanel <- function(x,y,...){
   panel.xyplot(x,y,...) #Scatter plot
   panel.lmline(x,y,type="l") #Regression line
}
```


With Custom Panel

```
xyplot(log(Ozone)~Solar.R | equal.count(Temp),
panel=mypanel, data=airquality)
```

Each panel shows a scatter plot (`panel.xyplot`) and a regression line (`panel.lmline`)

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)

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()`.

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.

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.

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

Distribution concepts: hazard function

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

$$\lambda(t) = P(t < T \leq t + \Delta | T > t)/\Delta, \ \ forsmall \Delta$$

$\approx$ 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

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

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:

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

Observed data on survival times

For individuals $i = 1, \ldots, n$ 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.

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 $\lambda(t)$.

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, δ_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.

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
```


Oral cancer: Kaplan-Meier estimates

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.

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.

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 $S(t) \neq F_1(t) + F_2(t)$

Event-specific quantities (cont'd)

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

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

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

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)

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
- $\delta_{ic} = 1_{\{T_i < U_i \ \& \ C_i = c\}}$, indicator (1/0) for event c being first observed, $c = 1, 2$.

Non-parametric estimation of CIF

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

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!

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.
```

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!

Ex. CIFs by cause in men and women

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

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:

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

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

$$\lambda_i(t) = \lambda_0(t)\exp(\eta_1),$$

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

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

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

PH model: interpretation of parameters

Present the model explicitly in terms of x's and β's.

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

Consider two individuals, i and i', having the same values of all other covariates except the jth 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 $e^{\beta_j} = \text{HR}_j =$ **hazard ratio** or relative rate associated with a unit change in covariate X_j.

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.

Predictions from the Cox model

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

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

- Having estimated β 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.

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`.

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

Representation of follow-up

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

SPE, Tartu, Estonia,

August 2019

http://BendixCarstensen.com/SPE

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.

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?

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

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

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

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

Probability	log-Likelihood
$\mathrm{P}(d \text{ at } t_x \mid \text{entry } t_0)$	$d\log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_0 \to t_1 \mid \text{entry } t_0)$	$= 0\log(\lambda_1) - \lambda_1 y_1$
$\times\, \mathrm{P}(\text{surv } t_1 \to t_2 \mid \text{entry } t_1)$	$+ 0\log(\lambda_2) - \lambda_2 y_2$
$\times\, \mathrm{P}(d \text{ at } t_x \mid \text{entry } t_2)$	$+ d\log(\lambda_3) - \lambda_3 y_3$

— allows different rates (λ_i) in each interval

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

Example: cohort with 3 persons:

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

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

Splitting the follow up

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

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

Splitting the follow-up

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

Keeping track of calendar time too?

Follow-up on several timescales

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

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

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

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

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
```

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:

exitdat - injecdat

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

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
```

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

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 )
```

EINLEITUNG

IN DIE

THEORIE

DER

BEVÖLKERUNGSSTATISTIK

VON

W. LEXIS

DR. DER STAATSWISSENSCHAFTEN UND DER PHILOSOPHIE,
O. PROFESSOR DER STATISTIK IN DORPAT.

STRASSBURG

KARL J. TRÜBNER

1875.

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
...
```

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
```

```
 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
```

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


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
```

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 Possion 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.

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.

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
 -------------------------------------
```

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

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

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
```

SMR

Bendix Carstensen

Representation of follow-up

SPE, Tartu, Estonia,

August 2019

http://BendixCarstensen.com/SPE

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)

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:

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

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

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:

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

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

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

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

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

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`)
- λ_{pop} is the population rate corresponding to the age, period and sex of the follow-up period y_i.

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
```



```
> 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
```

```
> 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
 ---------------------------------------------
```



```
 ---------------------------------------------
 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

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`

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 (± 2 y), and time of entry (± 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*

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 subchort 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*

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(IR):

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

- More refined analyses: Poisson or Cox regression.

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!

Estimation of hazard ratio

The incidence rate ratio can be expressed:

$$\text{IR} = \frac{D_1/D_0}{Y_1/Y_0} = \frac{\text{cases: exposed / unexposed}}{\text{person-times: exposed / unexposed}}$$

$$= \frac{\textit{exp're odds} \text{ in cases}}{\textit{exp're odds} \text{ in p-times}} = \textbf{exposure odds ratio} \text{ (EOR)}$$

= 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.

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 ($C << N$) from the population.
- Eligible controls must be bf risk (alive, under follow-up & free of outcome) at given time(s).

Study population in a case-control study?

Ideally: The study population comprises subjects who <u>*would be*</u> included as cases, <u>*if they got*</u> 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.

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.

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 – 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 Epidemology, 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!

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.

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 ρ without any "rare disease" assumption.

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** ρ.
- 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.

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 $\widehat{Y}_1/\widehat{Y}_0$, from estimated p-years.

Precision and efficiency

With exclusive **(A)** or concurrent **(C)** sampling of controls (unmatched), the estimated variance of log(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 ≥ 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.

$\Rightarrow$ Usually < 5 controls per case is enough.

$\Rightarrow$ *These designs are very cost-efficient!*

Estimation in concurrent or density sampling

- Assume a simple situation: Prevalence of exposure in the study population stable over time.

$\Rightarrow$ 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 EOR $= (D_1/D_0)/(C_1/C_0)$
  $=$ a consistent estimator of hazard ratio $\rho = \lambda_1/\lambda_0$.
- Variance of log(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).

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 ± 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.

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.

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 <u>is not similar</u> to the case w.r.t a correlate of exposure.

  ⇒ Increases efficiency!

  - Requires appropriate weighting in the analysis.

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.

Analysis of matched studies

- Close matching induces a new parameter for each matched case-control set or stratum.
  $\Rightarrow$ **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 β_js differs:

  (A) β_j = log of risk odds ratio (ROR),
  (C) β_j = log of hazard ratio (HR).

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 (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.

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.

Modelling in NCC and other matched studies

Cox proportional hazards model:

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

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

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

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

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

$\Leftrightarrow$ **Conditional logistic regression**
– function `clogit()` in `survival`, wrapper of `coxph()`.

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.

$\Rightarrow$ Ordinary Cox partial likelihood is wrong.

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

Correction method I – weighting

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

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

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.

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, $\rightarrow$ better comparability.

  CC: Measurements for subcohort performed at different times than for cases $\rightarrow$ 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.

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 infuenced by analytic batch, long-term storage, and freeze-thaw cycles.
- Matching helps in improving effciency and in reducing bias – but only if properly done.
- Handy R tools are available for all designs.

Some topics on causal inference

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Statistical Practice in Epidemiology, Tartu 2019

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

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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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?

None of these questions is “mathematical” enough to provide a mathematically correct definition of causal effect

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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
$$Y(X = 1) - Y(X = 0)$$
. where $Y(1) = Y(X = 1)$ and $Y(0) = Y(X = 0)$ are defined as individual's potential (counterfactual) outcomes if this individual's exposure level X were set to 1 or 0, respectively.
- Sometimes people (e.g J. Pearl) use the "do" notation to distinguish counterfactual variables from the observed ones: $Y(do(X = 1))$ and $Y(do(X = 0))$.

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The "naïve" association analysis

- With a binary exposure X, compare average outcomes in exposed and unexposed populations:

$$E(Y|X=1) - E(Y|X=0)$$

Is cancer incidence different in smokers and nonsmokers?

- But mostly:

$$E(Y|X=1) \neq E(Y(1))$$

Cancer risk in smokers is not the same as the potential cancer risk in the population if everyone were smoking

- Similarly:

$$E(Y|X=0) \neq E(Y(0))$$

- In most cases there is always some unobserved confounding present and therefore the naïve analysis does not provide causal effect estimates.

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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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 extremly 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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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.
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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!
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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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Instrumental variables estimation and Mendelian randomization

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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:

$$Y = \alpha_y + \beta X + \gamma U + \epsilon, \ \mathrm{E}(\epsilon|X, U) = 0$$

so $\mathrm{E}(Y|X) = \alpha_y + \beta X + \gamma \mathrm{E}(U|X)$.
Thus the coefficient of X will also depend on γ and the association between X and U.

General instrumental variables estimation

$$Y = \alpha_y + \beta X + \gamma U + \epsilon, \ \mathrm{E}(\epsilon|X, U) = 0$$

How can Z help?
If $\mathrm{E}(X|Z) = \alpha_x + \delta Z$, we get

$$\mathrm{E}(Y|Z) = \alpha_y + \beta E(X|Z) + \gamma E(U|Z) = \alpha_y + \beta(\alpha_x + \delta Z) = \alpha_y^* + \beta\delta Z.$$

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

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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()`.

Mendelian randomization example

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)

IV estimation in R (using `library(sem)`):

```
> 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 **
```


IV estimation: can untestable assumptions be tested?

```
> 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 *
```

Does FTO have a direct effect on Glc or T2D?
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:

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

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 $\beta_{pl} = 0$.
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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Multistate models

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Multistate models

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Common assumptions in survival analysis

1. Subjects are **either** "healthy" **or** "diseased", with no intermediate state.

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These assumptions are true for death and many chronic diseases.

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

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- length of stay (sojourn time)

Markov models for multistate diseases

Generalization of Poisson regression to multiple disease states:

Markov models for multistate diseases

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- 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

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Times should be recorded as **dates**

- birth date

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- exit date
- death date
- state entry date**s** — for all states

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

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

- λ_{psv} rate for person p in state s going to state v
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Practical multistate modeling

- Total log-lik is sum of terms over persons (p) and transitions ($s \to v$)
- — 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 with `Lexis`

Bendix Carstensen

Multistate models

SPE, Tartu, Estonia,

August 2019

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.

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

		Remission	
	Total	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

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.


```
> 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
```

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

Cutting follow-up at remission: cutLexis

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

Transitions:
     To
From  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
```


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 )
```

Splitting states: cutLexis

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

Transitions:
     To
From  NRA Rem ESRD ESRD(Rem)  Records:  Events: Risk time:  Persons:
  NRA  24  29   69         0       122       98     824.77       122
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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 )
```

Likelihood for a general MS-model

- Product of likelihoods for each transition
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- **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

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

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Modeling in a multistate model

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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(Ren)"), 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")) )
```

. . . using the Lexis properties

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```
> # 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
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+                       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

State probabilities

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

Simulation of a survival time

- For a rate function $\lambda(t)$, $\Lambda(t) = \int_0^t \lambda(s)\,\mathrm{d}s$:

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

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

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

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

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- 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.

Transition objects are glm/gam

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


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- Use nState to count how many persons in each state at different times

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
```

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
 48.655  52.448  36.065

> summary(sim1)

Transitions:
     To
From  NRA  Rem ESRD ESRD(Rem)  Records:  Events: Risk time:  Persons:
  NRA 293 1797 7910         0     10000     9707   74766.04     10000
  Rem   0  874    0       923      1797      923   19852.42      1797
  Sum 293 2671 7910       923     11797    10630   94618.45     10000
```


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  9955    20    25         0
  0.2  9889    46    65         0
  0.3  9837    75    88         0
  0.4  9779   104   117         0
  0.5  9732   127   140         1

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


Using a simulated Lexis object — pState II

```
     State
when     NRA    Rem ESRD(Rem) ESRD
  0   1.0000 1.0000    1.0000    1
  0.1 0.9955 0.9975    0.9975    1
  0.2 0.9889 0.9935    0.9935    1

> tail( nw1, 3 )

      State
when      NRA    Rem ESRD(Rem) ESRD
  14.8 0.1004 0.2165    0.2751    1
  14.9 0.0969 0.2128    0.2717    1
  15   0.0953 0.2101    0.2701    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] )
```

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 0.0020 0.9975    1
  0.2         0 0.0046 0.9935    1

> tail( nw2, 3 )

      State
when   ESRD(Rem)    Rem    NRA ESRD
  14.8    0.0586 0.1747 0.2751    1
  14.9    0.0589 0.1748 0.2717    1
  15      0.0600 0.1748 0.2701    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)] )
```


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

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

Precision of simulated probabilities

Multistate model overview

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- 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)