

# Statistical Analysis in the Lexis Diagram: Age-Period-Cohort models — and some cousins

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

European Doctoral School of Demography, Odense,  
June 2018

<http://BendixCarstensen/APC/EDSD-2018>

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## About the lectures

- ▶ Please interrupt:  
Most likely I did a mistake or left out a crucial argument.
- ▶ The handouts are not perfect  
— please comment on them,  
prospective students would benefit from it.
- ▶ Time-schedule:  
Two lectures ( $\approx 2$  hrs)  
one practical ( $\approx 1$  hr)

Introduction (intro)

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## Introduction

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Statistical Analysis in the  
Lexis Diagram:

Age-Period-Cohort models  
— and some cousins

European Doctoral School of Demography, Odense,  
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intro

## About the practicals

- ▶ You should use your preferred **R**-environment.
- ▶ Epi-package for **R** is needed, check that you have version 2.30
- ▶ Data are all on the course website.
- ▶ Try to make a text version of the answers to the exercises —  
it is more rewarding than just looking at output.  
The latter is soon forgotten — Rmd is a possibility.
- ▶ An opportunity to learn emacs, ESS and Sweave?

Introduction (intro)

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## Welcome

- ▶ Purpose of the course:
  - ▶ knowledge about APC-models
  - ▶ technical knowledge of handling them
  - ▶ insight in the basic concepts of analysis of rates
  - ▶ handling observation in the Lexis diagram
- ▶ Remedies of the course:
  - ▶ Lectures with handouts (BxC)
  - ▶ Practicals with suggested solutions (BxC)
  - ▶ Assignment for Thursday

Introduction (intro)

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## Rates and Survival

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surv-rate

## Scope of the course

- ▶ Rates as observed in populations  
— disease registers for example.
- ▶ Understanding of survival analysis (statistical analysis of rates)  
— this is the content of much of the first day.
- ▶ Besides concepts, practical understanding of the actual  
computations (in **R**) are emphasized.
- ▶ There is a section in the practicals:  
“Basic concepts of rates and survival”  
— read it; use it as reference.
- ▶ If you are not quite familiar with matrix algebra in **R**, there is  
an intro on the course homepage.

Introduction (intro)

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## Survival data

- ▶ Persons enter the study at some date.
- ▶ Persons exit at a later date, either dead or alive.
- ▶ Observation:
  - ▶ Actual time span to death (“event”)
  - ▶ ... or ...
  - ▶ Some time alive (“at least this long”)

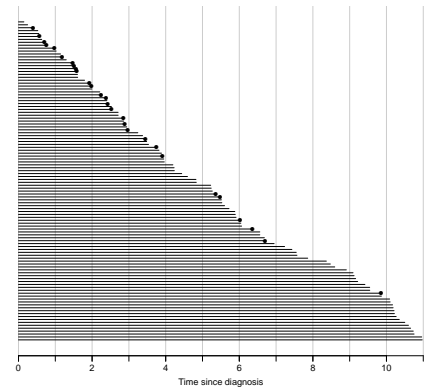
Rates and Survival (surv-rate)

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## Examples of time-to-event measurements

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

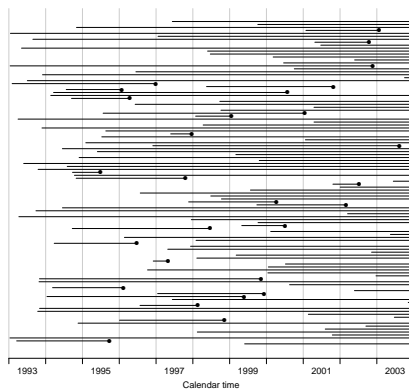
Patients ordered by survival time.



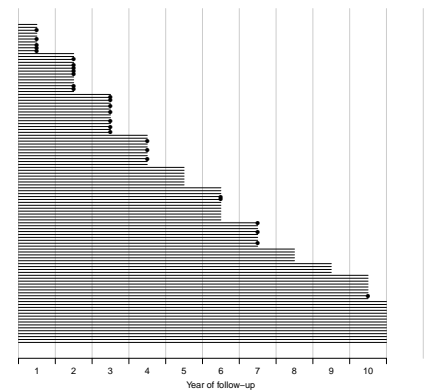
Each line a person

Each blob a death

Study ended at 31 Dec. 2003

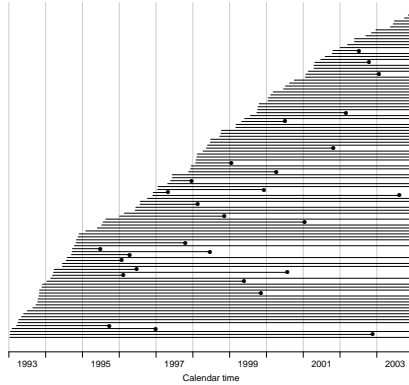


Survival times grouped into bands of survival.

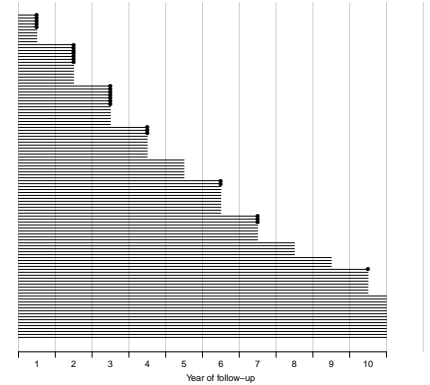


Ordered by date of entry

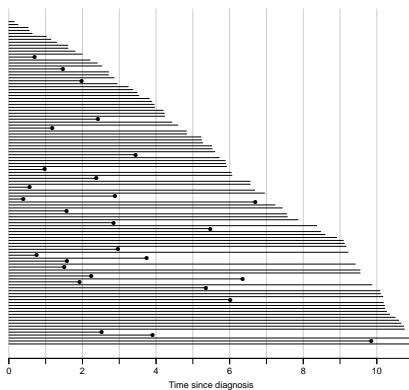
Most likely the order in your database.



Patients ordered by survival status within each band.



Timescale changed to "Time since diagnosis".



## Survival after Cervix cancer

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

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

Estimated 1 year survival is  $1 - 0.0465 = 0.9535$  — Life-table estimator.

## Survival function

Persons enter at time 0:

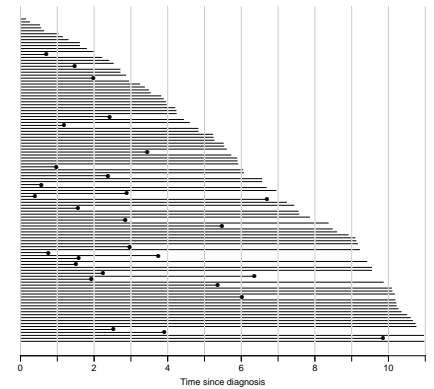
- Date of birth
- Date of randomization
- Date of diagnosis.

How **long** they survive, survival time  $T$  — a stochastic variable.

Distribution is characterized by the survival function:

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

Empirical rates by time since diagnosis.



## Intensity or rate

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

This is the **intensity** or **hazard function** for the distribution.

Characterizes the survival distribution as does  $f$  or  $F$ .

Theoretical counterpart of a **rate**.

## Two timescales

Note that we actually have two timescales:

- ▶ Time since diagnosis (*i.e.* since entry into the study)
- ▶ Calendar time.

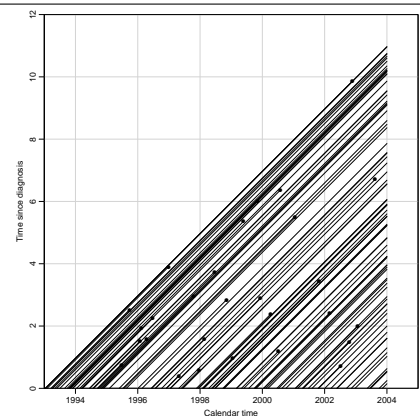
These can be shown simultaneously in a Lexis diagram.

## Empirical rates for individuals

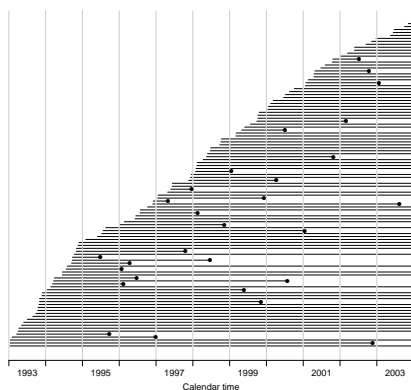
- ▶ At the **individual** level we introduce the **empirical rate**:  $(d, y)$ ,  
— no. of events ( $d \in \{0, 1\}$ ) during  $y$  risk time
- ▶ Each person may contribute several empirical  $(d, y)$
- ▶ Empirical rates are **responses** in survival analysis
- ▶ The timescale is a **covariate**:  
— that varies between empirical rates from one individual:  
Age, calendar time, time since diagnosis
- ▶ Do not confuse timescale with  
 $y$  — risk time (called exposure in demography)  
a **difference** between two points on **any** timescale

Follow-up by calendar time *and* time since diagnosis:

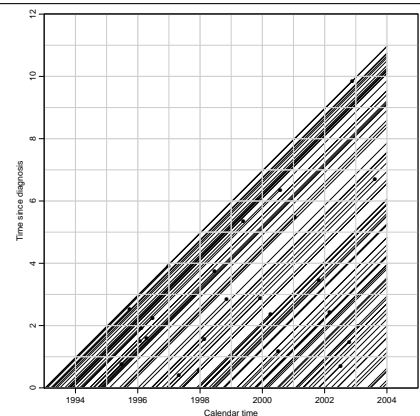
A Lexis diagram!



Empirical rates by calendar time.



Empirical rates by calendar time *and* time since diagnosis



## Likelihood for rates

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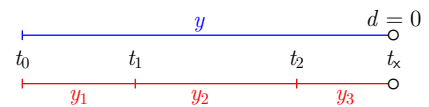
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likelihood



Probability

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

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

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

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

log-Likelihood

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

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

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

$$+ 0 \log(\lambda) - \lambda y_3$$

Likelihood for rates (likelihood)

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## Likelihood contribution from one person

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

$$P\{\text{event at } t_4 | \text{alive at } t_0\} = P\{\text{event at } t_4 | \text{alive at } t_3\} \times \\ P\{\text{survive } (t_2, t_3) | \text{alive at } t_2\} \times \\ P\{\text{survive } (t_1, t_2) | \text{alive at } t_1\} \times \\ P\{\text{survive } (t_0, t_1) | \text{alive at } t_0\}$$

Likelihood contribution from one individual is a **product** of terms.

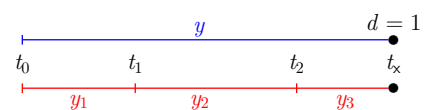
Each term refers to one empirical rate  $(d, y)$

with  $y = t_{i+1} - t_i$  (mostly  $d = 0$ ).

$t_i$  is a **covariate**

Likelihood for rates (likelihood)

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Probability

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

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

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

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

log-Likelihood

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

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

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

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

Likelihood for rates (likelihood)

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## Likelihood for an empirical rate

- ▶ Likelihood depends on **data** and the **model**
- ▶ Model: the rate  $(\lambda)$  is constant in the interval.
- ▶ The interval should be sufficiently small for this assumption to be reasonable.

$$L(\lambda | y, d) = P\{\text{survive } y\} \times P\{\text{event}\}^d \\ = e^{-\lambda y} \times (\lambda dt)^d \\ = \lambda^d e^{-\lambda y}$$

$$\ell(\lambda | y, d) = d \log(\lambda) - \lambda y$$

Likelihood for rates (likelihood)

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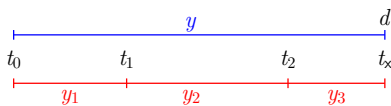
## Aim of dividing time into bands:

- ▶ Compute rates in different bands of:
  - ▶ age
  - ▶ calendar time
  - ▶ disease duration
  - ▶ ...
- ▶ Allow rates to vary along the timescale:

$$\begin{aligned} 0 \log(\lambda) - \lambda y_1 \\ + 0 \log(\lambda) - \lambda y_2 \\ + d \log(\lambda) - \lambda y_3 \end{aligned} \quad \rightarrow \quad \begin{aligned} 0 \log(\lambda_1) - \lambda_1 y_1 \\ + 0 \log(\lambda_2) - \lambda_2 y_2 \\ + d \log(\lambda_3) - \lambda_3 y_3 \end{aligned}$$

Likelihood for rates (likelihood)

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Probability

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

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

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

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

log-Likelihood

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

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

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

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

Likelihood for rates (likelihood)

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## Log-likelihood from more persons

- ▶ One person  $p$ , different times  $t$ :  $\sum_t (d_{pt} \log(\lambda_t) - \lambda_t y_{pt})$
- ▶ More persons:  $\sum_p \sum_t (d_{pt} \log(\lambda_t) - \lambda_t y_{pt})$
- ▶ Collect terms with identical values of  $\lambda_t$ :

$$\sum_t \sum_p (d_{pt} \log(\lambda_t) - \lambda_t y_{pt}) = \sum_t \left( \left( \sum_p d_{pt} \right) \log(\lambda_t) - \lambda_t \sum_p y_{pt} \right) \\ = \sum_t \left( D_t \log(\lambda_t) - \lambda_t Y_t \right)$$

- ▶ All events in interval  $t$  ("at" time  $t$ ),  $D_t$
- ▶ All exposure time in interval  $t$  ("at" time  $t$ ),  $Y_t$

Likelihood for rates (likelihood)

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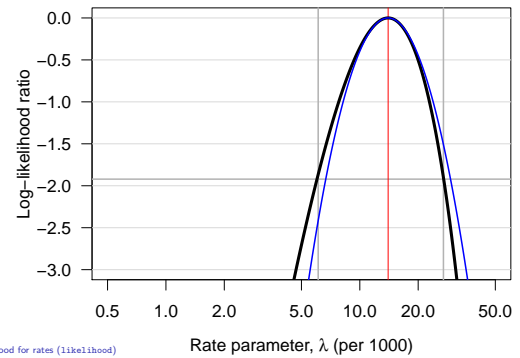
### Likelihood example

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

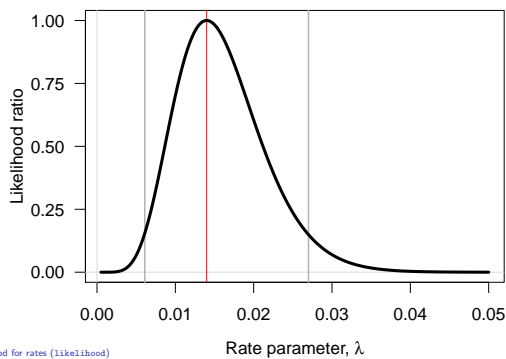
$$\begin{aligned} P\{D = 7, Y = 500|\lambda\} &= \lambda^D e^{-\lambda Y} \times K \\ &= \lambda^7 e^{-\lambda 500} \times K \\ &= L(\lambda|\text{data}) \end{aligned}$$

- ▶ Best guess of  $\lambda$  is where this function is as large as possible.
- ▶ Confidence interval is where it is not too far from the maximum

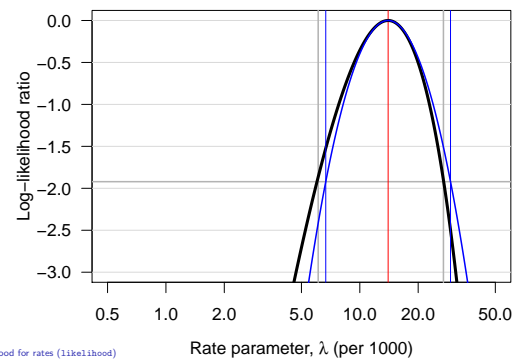
### Log-likelihood ratio



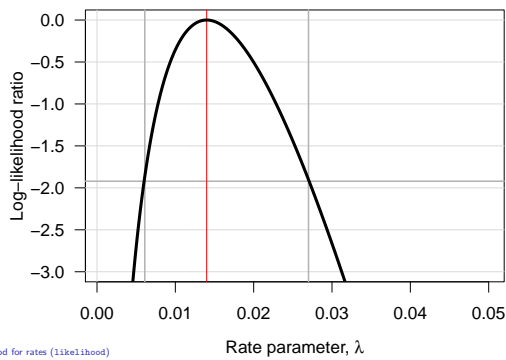
### Likelihood-ratio function



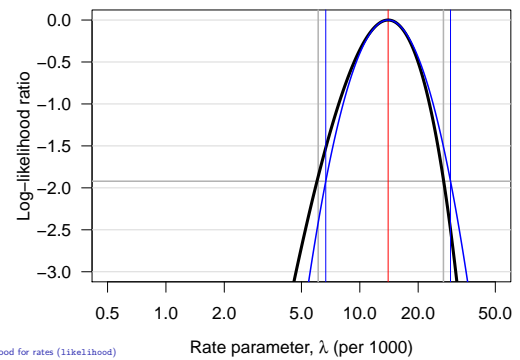
### Log-likelihood ratio



### Log-likelihood ratio

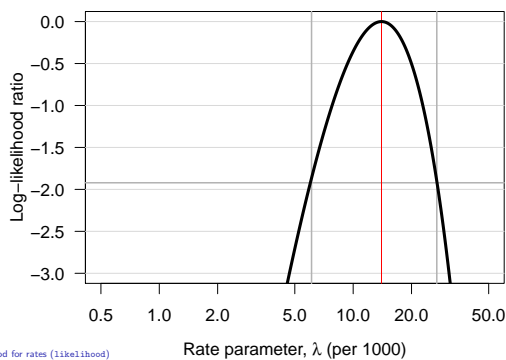


### Log-likelihood ratio



$$\begin{aligned} \hat{\lambda} &= 7/500 = 14 \\ \hat{\lambda} \times & \exp(1.96/\sqrt{7}) = \\ & (6.7, 29.4) \end{aligned}$$

### Log-likelihood ratio



### Poisson likelihood

Log-likelihood from **follow-up** of **one individual**,  $p$ , in interval  $t$ :

$$\ell_{FU}(\lambda|d, y) = d_{pt} \log(\lambda(t)) - \lambda(t) y_{pt}, \quad t = 1, \dots, t_p$$

Log-likelihood from a **Poisson observation**  $d_{pt}$  with mean  $\mu = \lambda(t) y_{pt}$ :

$$\begin{aligned} \ell_{Poisson}(\lambda y|d) &= d_{pt} \log(\lambda(t) y_{pt}) - \lambda(t) y_{pt} \\ &= \ell_{FU}(\lambda|d, y) + d_{pt} \log(y_{pt}) \end{aligned}$$

**Extra term** does not depend on the rate parameter  $\lambda$ .

## Poisson likelihood

Log-likelihood contribution from **one** individual,  $p$ , say, is:

$$\ell_{\text{FU}}(\lambda|d, y) = \sum_t (d_{pt} \log(\lambda(t)) - \lambda(t)y_{pt})$$

- ▶ The terms in the sum are **not** independent,
  - ▶ but the log-likelihood is a **sum** of Poisson-like terms,
  - ▶ the **same** as a likelihood for **independent** Poisson variates,  $d_{pt}$
  - ▶ with mean  $\mu = \lambda_t y_{pt} \Leftrightarrow \log \mu = \log(\lambda_t) + \log(y_{pt})$
- ⇒ Analyse rates  $\lambda$  based on empirical rates  $(d, y)$  as a Poisson model for independent variates where:
- ▶  $d_{pt}$  is the response variable.
  - ▶  $\log(y_{pt})$  is the offset variable.

Likelihood for rates (likelihood)

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## Confidence interval for a rate

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

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

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

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

Alternatively do the c.i. directly on the rate scale:

$$\lambda \pm 1.96\sqrt{D}/Y$$

Likelihood for rates (likelihood)

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## Likelihood for follow-up of many subjects

Adding empirical rates over the follow-up of persons:

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

- ▶ Persons are assumed independent
- ▶ Contribution from the same person are **conditionally** independent, hence give separate contributions to the log-likelihood.
- ▶ Follow-up **model** and Poisson **model** are different
- ▶ ... but the **likelihoods** are the same.

Likelihood for rates (likelihood)

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## Exercise

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

Calculate the mortality rate with a 95% c.i.

Likelihood for rates (likelihood)

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The log-likelihood is maximal for:

$$\frac{d\ell(\lambda)}{d\lambda} = \frac{D}{\lambda} - Y = 0 \quad \Leftrightarrow \quad \hat{\lambda} = \frac{D}{Y}$$

Information about the log-rate  $\theta = \log(\lambda)$ :

$$\ell(\theta|D, Y) = D\theta - e^\theta Y, \quad \ell'_\theta = D - e^\theta Y, \quad \ell''_\theta = -e^\theta Y$$

so  $I(\hat{\theta}) = e^{\hat{\theta}} Y = \hat{\lambda} Y = D$ , hence  $\text{var}(\hat{\theta}) = 1/D$

Standard error of log-rate:  $1/\sqrt{D}$ .

Note that this only depends on the no. events, **not** on the follow-up time.

Likelihood for rates (likelihood)

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## Rates with glm

```
> library(Epi)
> D <- 17
> Y <- 843.6/1000
> round( ci.exp( glm( D ~ 1, offset=log(Y), family=poisson ), 2 )
      exp(Est.) 2.5% 97.5%
(Intercept) 20.15 12.53 32.42
> round( ci.exp( glm( D/Y ~ 1, weight= Y, family=poisson ), 2 )
      exp(Est.) 2.5% 97.5%
(Intercept) 20.15 12.53 32.42
> round( ci.exp( glm( D/Y ~ 1, weight= Y, family=poisson(link="identity"),
+               Exp=FALSE), 2 )
      Estimate 2.5% 97.5%
(Intercept) 20.15 10.57 29.73
```

Likelihood for rates (likelihood)

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The log-likelihood is maximal for:

$$\frac{d\ell(\lambda)}{d\lambda} = \frac{D}{\lambda} - Y = 0 \quad \Leftrightarrow \quad \hat{\lambda} = \frac{D}{Y}$$

Information about the rate itself,  $\lambda$ :

$$\ell(\lambda|D, Y) = D \log(\lambda) - \lambda Y \quad \ell'_\lambda = \frac{D}{\lambda} - Y \quad \ell''_\lambda = -\frac{D}{\lambda^2}$$

so  $I(\hat{\lambda}) = D/\hat{\lambda}^2 = Y^2/D$ , hence  $\text{var}(\hat{\lambda}) = D/Y^2$

Standard error of a rate:  $\sqrt{D}/Y$ .

Likelihood for rates (likelihood)

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## Ratio of two rates

If we have observations two rates  $\lambda_1$  and  $\lambda_0$ , based on  $(D_1, Y_1)$  and  $(D_0, Y_0)$  the variance of the log of the ratio of the rates,  $\log(\text{RR})$ , is:

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

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

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

Likelihood for rates (likelihood)

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## Exercise

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

Calculate the rate-ratio between group 1 and 0 with a 95% c.i.

## Rate-ratio with glm

```
> library(Epi)
> D <- c(17,28)
> Y <- c(843.6,632.3)/1000
> F <- factor(0:1)
> round( ci.exp( glm( D ~ F, offset=log(Y), family=poisson ) ), 2 )

      exp(Est.)  2.5% 97.5%
(Intercept)  20.15 12.53 32.42
F1           2.20  1.20  4.01

> round( ci.exp( glm( D ~ F - 1, offset=log(Y), family=poisson ) ), 2 )

      exp(Est.)  2.5% 97.5%
F0           20.15 12.53 32.42
F1           44.28 30.58 64.14
```

## Rate-ratio and -difference with glm

```
> round( ci.exp( glm( D/Y ~ F , weight=Y, family=poisson ) ), 2 )

      exp(Est.)  2.5% 97.5%
(Intercept)  20.15 12.53 32.42
F1           2.20  1.20  4.01

> round( ci.exp( glm( D/Y ~ F , weight=Y, family=poisson(link="identity")),
+               Exp=FALSE), 2 )

      Estimate  2.5% 97.5%
(Intercept)  20.15 10.57 29.73
F1           24.13  5.14 43.13

> round( ci.exp( glm( D/Y ~ F - 1, weight=Y, family=poisson(link="identity")),
+               Exp=FALSE), 2 )

      Estimate  2.5% 97.5%
F0           20.15 10.57 29.73
F1           44.28 27.88 60.69
```

# Lifetables

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## The life table method

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

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

$$p_i = P \{ \text{death in interval } i \} = 1 - d_i / (n_i - l_i / 2)$$

$$S(t) = (1 - p_1) \times \dots \times (1 - p_t)$$

## The life table method

The life-table method computes survival probabilities for each time interval, in demography normally one year.

The rate is the number of deaths  $d_i$  divided by the risk time  $(n_i - d_i/2 - l_i/2) \times \ell_i$ :

$$\lambda_i = \frac{d_i}{(n_i - d_i/2 - l_i/2) \times \ell_i}$$

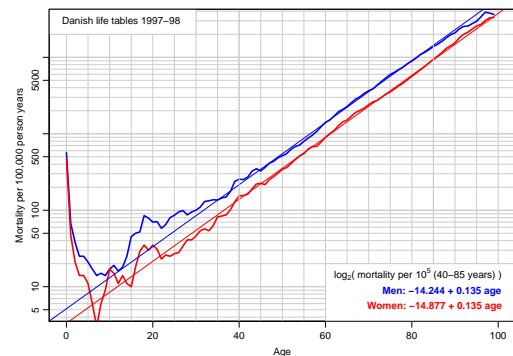
and hence the death probability:

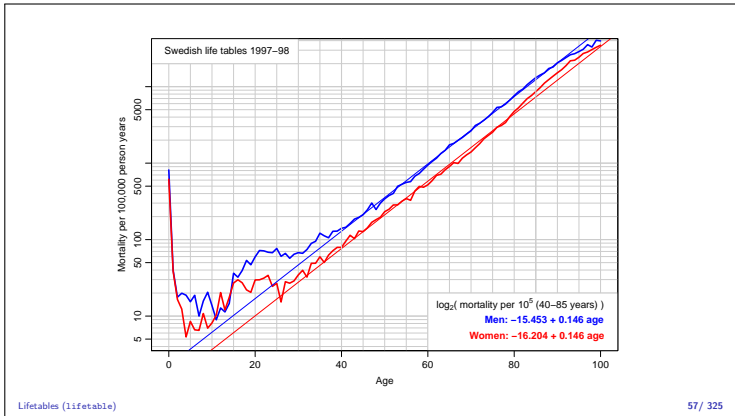
$$p_i = 1 - \exp(-\lambda_i \ell_i) = 1 - \exp\left(-\frac{d_i}{(n_i - d_i/2 - l_i/2)}\right)$$

The modified life-table estimator.

## Population life table, DK 1997–98

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





### Life table approach

The observation of interest is **not** the survival time of the **individual**.

It is the **population** experience:

- $D$ : Deaths (events).
- $Y$ : Person-years (risk time).

The classical lifetable analysis compiles these for prespecified intervals of age, and computes age-specific mortality **rates**.

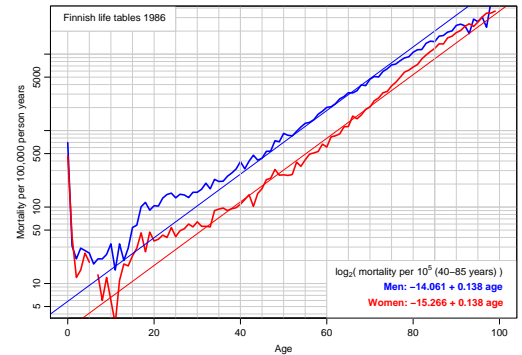
Data are collected cross-sectionally, but interpreted longitudinally.

### Practical

Based on the previous slides answer the following for both Danish and Swedish lifetables:

- ▶ What is the doubling time for mortality?
- ▶ What is the rate-ratio between males and females?
- ▶ How much older should a woman be in order to have the same mortality as a man?

### Rates vary over time:

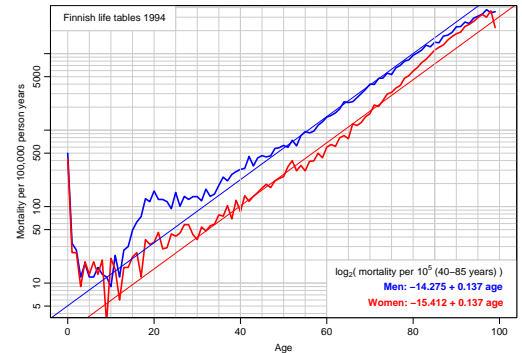


Denmark	Males	Females
$\log_2(\lambda(a))$	$-14.244 + 0.135 \text{ age}$	$-14.877 + 0.135 \text{ age}$
Doubling time	$1/0.135 = 7.41 \text{ years}$	
M/F rate-ratio	$2^{-14.244+14.877} = 2^{0.633} = 1.55$	
Age-difference	$(-14.244 + 14.877)/0.135 = 4.69 \text{ years}$	

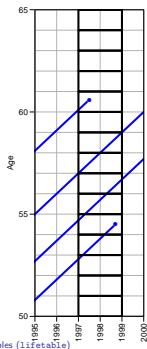
  

Sweden:	Males	Females
$\log_2(\lambda(a))$	$-15.453 + 0.146 \text{ age}$	$-16.204 + 0.146 \text{ age}$
Doubling time	$1/0.146 = 6.85 \text{ years}$	
M/F rate-ratio	$2^{-15.453+16.204} = 2^{0.751} = 1.68$	
Age-difference	$(-15.453 + 16.204)/0.146 = 5.14 \text{ years}$	

### Rates vary over time:



### Observations for the lifetable



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

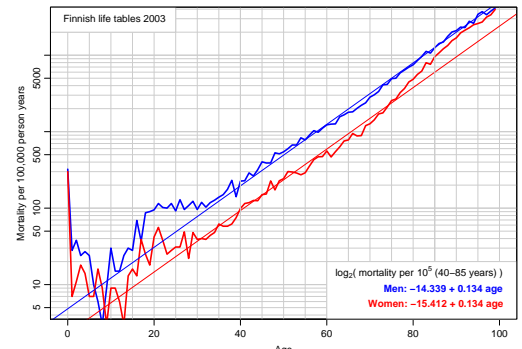
Age-specific rates — cross-sectional!

Survival function:

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

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

### Rates vary over time:





# Who needs the Cox-model anyway?

**Bendix Carstensen**

Statistical Analysis in the  
Lexis Diagram:

Age-Period-Cohort models  
— and some cousins

European Doctoral School of Demography, Odense,  
June 2018

<http://BendixCarstensen/APC/EDSD-2018>

KMCoX

## Splitting the dataset a priori

- ▶ The Poisson approach needs a dataset of empirical rates  $(d, y)$  with suitably small values of  $y$ .
- ▶ — each individual contributes many empirical rates
- ▶ (one per risk-set contribution in Cox-modelling)
- ▶ From each empirical rate we get:
  - ▶ Poisson-response  $d$
  - ▶ Risk time  $y \rightarrow \log(y)$  as offset
  - ▶ time scale covariates: current age, current date, ...
  - ▶ other covariates
- ▶ Contributions not independent, but likelihood is a product
- ▶ Same likelihood as for independent Poisson variates
- ▶ Poisson glm with spline/factor effect of time

Who needs the Cox-model anyway? (KMCoX)

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## A look at the Cox model

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

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

Covariates:

- ▶  $x$
- ▶  $t$
- ▶ ... often the effect of  $t$  is ignored (forgotten?)
- ▶ i.e. left unreported

Who needs the Cox-model anyway? (KMCoX)

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## Example: Mayo Clinic lung cancer

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

Who needs the Cox-model anyway? (KMCoX)

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## The Cox-likelihood as profile likelihood

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

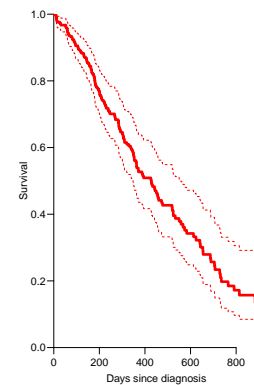
$$\log(\lambda(t, x_i)) = \log(\lambda_0(t)) + \underbrace{\beta_1 x_{1i} + \dots + \beta_p x_{pi}}_{\eta_i} = \alpha_t + \eta_i$$

- ▶ Profile likelihood:
  - ▶ Derive estimates of  $\alpha_t$  as function of data and  $\beta$ s — assuming constant rate between death/censoring times
  - ▶ Insert in likelihood, now only a function of data and  $\beta$ s
  - ▶ This turns out to be Cox's partial likelihood
- ▶ Cumulative intensity  $(\Lambda_0(t))$  obtained via the Breslow-estimator

Who needs the Cox-model anyway? (KMCoX)

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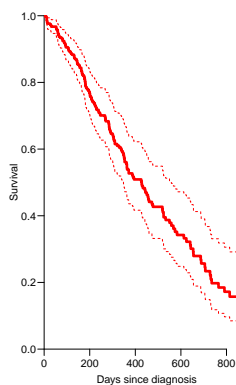
## Mayo Clinic lung cancer 60 year old woman



Who needs the Cox-model anyway? (KMCoX)

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## Mayo Clinic lung cancer data: 60 year old woman



Who needs the Cox-model anyway? (KMCoX)

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## Example: Mayo Clinic lung cancer I

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

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

```
> summary( Lung )
```

```
Transitions:
To
From Alive Dead Records Events Risk time: Persons:
Alive 63 165 228 165 69593 228
```

Who needs the Cox-model anyway? (KMCoX)

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## Example: Mayo Clinic lung cancer II

```
> system.time(
+ mL.cox <- coxph( Surv( tfe, tfe+lex.dur, lex.Xst=="Dead" ) ~
+ age + factor( sex ),
+ method="breslow", data=Lung ) )

user system elapsed
0.008 0.003 0.009

> Lung.s <- splitLexis( Lung,
+ breaks=c(0,sort(unique(Lung$time))),
+ time.scale="tfe" )
> summary( Lung.s )

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

> subset( Lung.s, lex.id==96 )[,1:11] ; nlevels( factor( Lung.s$tfe ) )
```

Who needs the Cox-model anyway? (RXCox)

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## Example: Mayo Clinic lung cancer VI

```
> round( cmp, 7 )

          age 2.5% 97.5% sex 2.5% 97.5%
Cox      1.017158 0.9989388 1.035710 0.5989574 0.4313720 0.8316487
Poisson-factor 1.017158 0.9989388 1.035710 0.5989574 0.4313720 0.8316487
Poisson-spline 1.016189 0.9980329 1.034676 0.5998287 0.4319932 0.8328707
Poisson-Pspline 1.016418 0.9982551 1.034912 0.6032132 0.4345782 0.8372858
```

Who needs the Cox-model anyway? (RXCox)

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## Example: Mayo Clinic lung cancer III

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

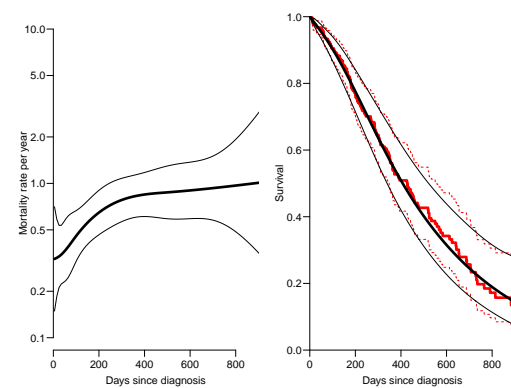
[1] 186

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

user system elapsed
13.611 17.990 9.213
```

Who needs the Cox-model anyway? (RXCox)

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Who needs the Cox-model anyway? (RXCox)

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## Example: Mayo Clinic lung cancer IV

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

[1] 188

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

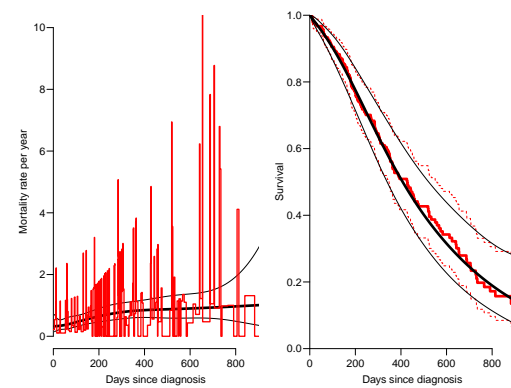
[1] 20022 4

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

user system elapsed
0.444 0.447 0.292
```

Who needs the Cox-model anyway? (RXCox)

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Who needs the Cox-model anyway? (RXCox)

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## Example: Mayo Clinic lung cancer V

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

user system elapsed
0.914 1.303 0.612

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

Who needs the Cox-model anyway? (RXCox)

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## Deriving the survival function

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

> CM <- cbind( 1, Ns( seq(10,1000,10)-5, knots=t.kn ), 60, 1 )
> lambda <- ci.exp( mLs.pois.sp, ctr.mat=CM )
> Lambda <- ci.cum( mLs.pois.sp, ctr.mat=CM, int1=10 ) [ , -4 ]
> survP <- exp(-rbind(0, Lambda))
```

Code and output for the entire example available in  
<http://bendixcarstensen.com/AdvCoh/WNtCMa/>

Who needs the Cox-model anyway? (RXCox)

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## What the Cox-model really is

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

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

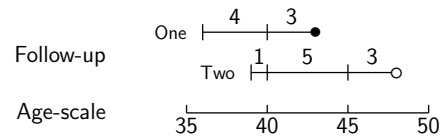
Code and output for the entire example available in <http://bendixcarstensen.com/AdvCoh/WNtCMA/>

## Examples: stratification by age

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

If follow-up is long, use stratification by categories of **current age**, both for:

No. of events,  $D$ , and Risk time,  $Y$ .



— assuming a constant rate  $\lambda$  throughout.

## Models of this world

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

## Representation of follow-up data

A cohort or follow-up study records:

**Events and Risk time.**

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

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

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

Specific for each **type** of outcome.

## Follow-up data

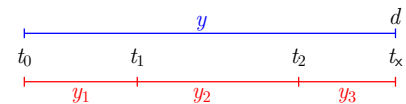
### Bendix Carstensen

Statistical Analysis in the Lexis Diagram:

Age-Period-Cohort models  
 — and some cousins

European Doctoral School of Demography, Odense,  
 June 2018

<http://BendixCarstensen/APC/EDSD-2018>



Probability

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

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

log-Likelihood

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

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

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

## Follow-up and rates

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

## 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.

Follow-up data (time-split)

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## Timescales

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

Follow-up data (time-split)

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## Splitting the follow up

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

Follow-up data (time-split)

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## Follow-up on several timescales

- ▶ The risk-time is the same on all timescales
- ▶ Only need the entry point on each time scale:
  - ▶ Age at entry.
  - ▶ Date of entry.
  - ▶ Time since treatment at entry.
    - if time of treatment is the entry, this is 0 for all.
- ▶ **Response variable** in analysis of rates:
 
$$(d, y) \quad (\text{event, duration})$$
- ▶ **Covariates** in analysis of rates:
  - ▶ timescales
  - ▶ other (fixed) measurements
- ▶ ... do not confuse **duration** and **timescale** !

Follow-up data (time-split)

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Age	subj. 1		subj. 2		subj. 3		$\Sigma$	
	<i>Y</i>	<i>D</i>	<i>Y</i>	<i>D</i>	<i>Y</i>	<i>D</i>	<i>Y</i>	<i>D</i>
0-	0.00	0	0.00	0	5.46	0	5.46	0
10-	6.94	0	1.56	0	1.12	1	8.62	1
20-	10.00	0	10.00	0	0.00	0	20.00	0
30-	10.00	0	10.00	0	0.00	0	20.00	0
40-	4.95	1	1.14	0	0.00	0	6.09	1
$\Sigma$	31.89	1	22.70	0	6.58	1	60.17	2

Follow-up data (time-split)

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## Follow-up data in Epi — Lexis objects

```
> 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 (time-split)

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## Splitting the follow-up

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

Keeping track of calendar time too?

Follow-up data (time-split)

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## Definition of Lexis object

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

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

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

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

Follow-up data (time-split)

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## The looks of a Lexis object

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

> summary( thL )
Transitions:
  To
From  0  1 Records:  Events:  Risk time:  Persons:
  0 504 1964    2468    1964    51934.08    2468
```

Follow-up data (time-split)

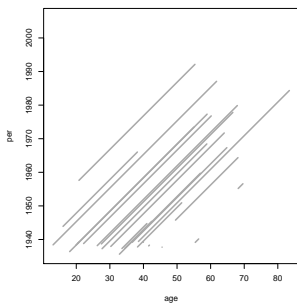
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## Splitting follow-up time

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

Follow-up data (time-split)

95/ 325



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

Follow-up data (time-split)

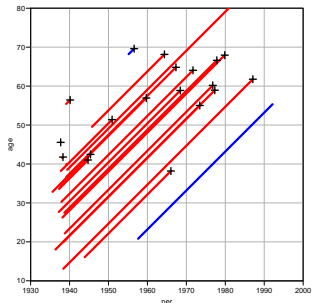
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## Split on another timescale

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

Follow-up data (time-split)

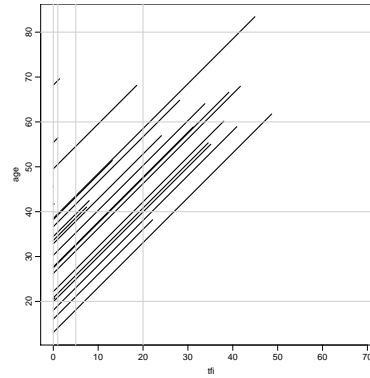
96/ 325



```
> 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 )
```

Follow-up data (time-split)

94/ 325



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

Follow-up data (time-split)

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

## Likelihood for a constant rate

- ▶ This setup is for a situation where it is assumed that rates are constant in each of the intervals.
- ▶ Each observation in the dataset contributes a term to the likelihood.
- ▶ Each term looks like a contribution from a Poisson variate (albeit with values only 0 or 1)
- ▶ Rates can vary along several timescales simultaneously.
- ▶ Models can include fixed covariates, as well as the timescales (the left end-points of the intervals) as continuous variables.
- ▶ The latter is where we will need splines.

Follow-up data (time-split)

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EINLEITUNG  
 IN DIE  
 THEORIE  
 DER  
 BEVÖLKERUNGSSTATISTIK  
 VON  
 W. LEXIS  
 DR. DER STAATSWISSENSCHAFT UND DER POLITIKWISSENSCHAFT,  
 O. PROFESSOR DER STATISTIK AN DER UNIVERSITÄT  
 STRASSBURG  
 KARL J. TREUBNER  
 DRUCK.



Follow-up data (time-split)

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## The Poisson likelihood for split data

- Split records (one per person-interval  $(p, i)$ ):

$$\sum_{p,i} (d_{pi} \log(\lambda) - \lambda y_{pi}) = D \log(\lambda) - \lambda Y$$

- Assuming that the death indicator ( $d_{pi} \in \{0, 1\}$ ) is Poisson, a model with with offset  $\log(y_{pi})$  will give the same result.
- If we assume that rates are constant we get the simple expression with  $(D, Y)$
- ... but the split data allows models that assume different rates for different  $(d_{pi}, y_{pi})$ , so rates can vary **within** a person's follow-up.

Follow-up data (time-split)

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## Fitting a simple model

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

contrast	D	Y	Rate
1	928.00	20094.74	4.62
2	1036.00	31822.24	3.26
Total	1964.00	51916.98	3.78

Follow-up data (time-split)

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

```
> spl1 <- splitLexis( thL , breaks=seq(0,100,20) , time.scale="age" )
> spl2 <- splitLexis( spl1, breaks=c(0,1,5,20,100), time.scale="tfi" )
> options( digits=5 )
> spl2[1:10,1:11]
```

lex.id	age	per	tfi	lex.dur	lex.Cst	lex.Xst	id	sex	birthdat	contrast
1	22.182	1938.8	0.000	1.00000	0	0	1	2	1916.6	1
2	23.182	1939.8	1.000	4.00000	0	0	1	2	1916.6	1
3	27.182	1943.8	5.000	12.81793	0	0	1	2	1916.6	1
4	40.000	1956.6	17.818	2.18207	0	0	1	2	1916.6	1
5	42.182	1958.8	20.000	17.81793	0	0	1	2	1916.6	1
6	60.000	1976.6	37.818	0.17796	0	1	1	2	1916.6	1
7	216.063	1943.9	0.000	1.00000	0	0	2	2	1927.8	1
8	217.063	1944.9	1.000	2.93703	0	0	2	2	1927.8	1
9	220.000	1947.8	3.937	1.06297	0	0	2	2	1927.8	1
10	221.063	1948.9	5.000	15.00000	0	0	2	2	1927.8	1

— and what are covariates for the rates?

Follow-up data (time-split)

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## Fitting a simple model

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

factor(contrast)	exp(Est.)	2.5%	97.5%
factor(contrast)1	4.62	4.33	4.93
factor(contrast)2	3.26	3.06	3.46

Follow-up data (time-split)

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

```
> library( popEpi )
> spl1 <- splitMulti( thL , age=seq(0,100,20) )
> spl2 <- splitMulti( spl1, tfi=c(0,1,5,20,100) )
> options( digits=5 )
> spl2[1:10,1:11]
```

lex.id	age	per	tfi	lex.dur	lex.Cst	lex.Xst	id	sex	birthdat	contrast
1:	22.182	1938.8	0.000	1.00000	0	0	1	2	1916.6	1
2:	23.182	1939.8	1.000	4.00000	0	0	1	2	1916.6	1
3:	27.182	1943.8	5.000	12.81793	0	0	1	2	1916.6	1
4:	40.000	1956.6	17.818	2.18207	0	0	1	2	1916.6	1
5:	42.182	1958.8	20.000	17.81793	0	0	1	2	1916.6	1
6:	60.000	1976.6	37.818	0.17796	0	1	1	2	1916.6	1
7:	216.063	1943.9	0.000	1.00000	0	0	2	2	1927.8	1
8:	217.063	1944.9	1.000	2.93703	0	0	2	2	1927.8	1
9:	220.000	1947.8	3.937	1.06297	0	0	2	2	1927.8	1
10:	221.063	1948.9	5.000	15.00000	0	0	2	2	1927.8	1

— not the printing: it's a data.table

Follow-up data (time-split)

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## Models for tabulated data

### Bendix Carstensen

Statistical Analysis in the Lexis Diagram:

Age-Period-Cohort models  
— and some cousins

European Doctoral School of Demography, Odense, June 2018

<http://BendixCarstensen/APC/EDSD-2018>

tab-mod

## Analysis of results

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

Follow-up data (time-split)

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## Conceptual set-up

Follow-up of the entire (male) population from 1943–2006 w.r.t. occurrence of testiscancer:

- Split follow-up time for all about 4 mio. men in 1-year classes by age and calendar time ( $y$ ).
- Allocate testis cancer event ( $d = 0, 1$ ) to each.
- Analyse all 200,000,000 records by a Poisson model.

Models for tabulated data (tab-mod)

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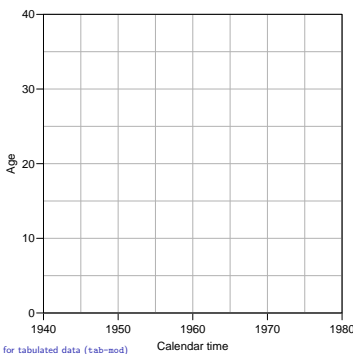
## Realistic set-up

- ▶ Tabulate the follow-up time and events by age and period.
- ▶ 100 age-classes.
- ▶ 65 periods (single calendar years).
- ▶ 6500 aggregate records of  $(D, Y)$ .
- ▶ Analyze by a Poisson model.

## Practical set-up

- ▶ Tabulate only events (as obtained from the cancer registry) by age and period.
- ▶ 100 age-classes.
- ▶ 65 periods (single calendar years).
- ▶ 6500 aggregate records of  $D$ .
- ▶ Estimate the population follow-up based on census data from Statistics Denmark ( $Y_{pop}$ ).  
... or get it from the human mortality database.
- ▶ If disease is common: tabulate follow-up **after** diagnosis ( $Y_{dis}$ ), and subtract from population follow-up.
- ▶ Analyse  $(D, Y)$  by Poisson model.

## Lexis diagram <sup>1</sup>

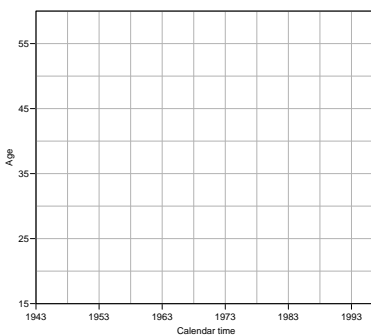


Disease registers record events.

Official statistics collect population data.

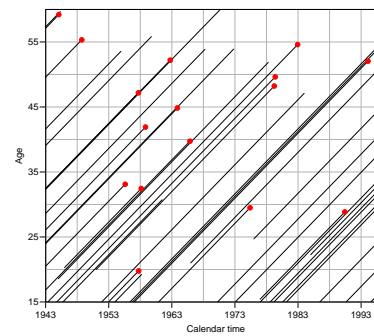
<sup>1</sup> Named after the German statistician and economist **William Lexis** (1837-1914), who devised this diagram in the book "Einführung in die Theorie der Bevölkerungsstatistik" (Karl J. Trübner, Strassburg, 1915).

## Lexis diagram



Registration of:  
cases ( $D$ )  
risk time,  
person-years ( $Y$ )  
in subsets of the Lexis diagram.

## Lexis diagram



Registration of:  
cases ( $D$ )  
risk time,  
person-years ( $Y$ )  
in subsets of the Lexis diagram.  
Rates available in each subset.

## Register data

Classification of **cases** ( $D_{ap}$ ) by age at diagnosis and date of diagnosis, and **population** ( $Y_{ap}$ ) by age at risk and date at risk, in compartments of the Lexis diagram, e.g.:

```
> fCtable( xtabs( cbind(D,Y) ~ A + P, data=ts ), col.vars=3:2, w=8 )
```

	D		Y					
P	1943	1948	1953	1958	1943	1948	1953	1958
A								
15	2	3	4	1	773,812	744,217	794,123	972,853
20	7	7	17	8	813,022	744,706	721,810	770,859
25	28	23	26	35	790,501	781,827	722,968	698,612
30	28	43	49	51	799,293	774,542	769,298	711,596
35	36	42	39	44	769,356	782,893	760,213	760,452
40	24	32	46	53	694,073	754,322	768,471	749,912

## In analysis format:

```
> ts
      A  P  D      Y
1  15 1943 2 773812
2  20 1943 7 813022
3  25 1943 28 790501
4  30 1943 28 799293
5  35 1943 36 769356
6  40 1943 24 694073
7  15 1948 3 744217
8  20 1948 7 744706
9  25 1948 23 781827
10 30 1948 43 774542
11 35 1948 42 782893
12 40 1948 32 754322
13 15 1953 4 794123
14 20 1953 17 721810
15 25 1953 26 722968
16 30 1953 49 769298
17 35 1953 39 760213
18 40 1953 46 768471
19 45 1958 1 672852
```

## Tabulated data

Once data are in tabular form, models are restricted:

- ▶ Rates must be assumed constant in each cell of the table / subset of the Lexis diagram.
- ▶ With large cells ( $5 \times 5$  years) it is customary to put a separate parameter on each cell or on each levels of classifying factors.
- ▶ Output from the model will be rates and rate-ratios.
- ▶ Since we use multiplicative Poisson, usually the log rates and the log-RR are reported

### Simple age-period model for the testiscancer rates:

```
> m0 <- glm( D ~ factor(A) + factor(P) + offset(log(Y/10^5)),
+           family=poisson, data=ts )
> summary( m0 )
```

```
Call:
glm(formula = D ~ factor(A) + factor(P) + offset(log(Y/10^5)),
    family = poisson, data = ts)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.5991 -0.6974  0.1284  0.6671  1.8904
```

```
Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  -1.4758    0.3267  -4.517 6.26e-06
factor(A)20    1.4539    0.3545   4.101 4.11e-05
factor(A)25    2.5321    0.3301   7.671 1.71e-14
factor(A)30    2.9327    0.3254   9.013 < 2e-16
factor(A)35    2.8613    0.3259   8.779 < 2e-16
factor(A)40    2.8521    0.3263   8.741 < 2e-16
factor(P)1948  0.1753    0.1211   1.447 0.14778
factor(P)1953  0.3822    0.1163   3.286 0.00102
factor(P)1958  0.4666    0.1155   4.042 0.00004
```

ci.exp() from the Epi package extracts coefficients and computes confidence intervals:

```
> round( ci.exp( m0 ), 2 )

             exp(Est.) 2.5% 97.5%
(Intercept)      0.23 0.12 0.43
factor(A)20      4.28 2.14 8.57
factor(A)25     12.58 6.59 24.02
factor(A)30     18.78 9.92 35.53
factor(A)35     17.49 9.23 33.12
factor(A)40     17.32 9.14 32.84
factor(P)1948    1.19 0.94 1.51
factor(P)1953    1.47 1.17 1.84
factor(P)1958    1.59 1.27 2.00
```

... what do these parameters mean?

Subsets of parameter estimates accessed via a character string that is grep-ed to the names.

```
> round( ci.exp( m0, subset="P", pval=TRUE ), 3 )

             exp(Est.) 2.5% 97.5%      P
factor(P)1948    1.192 0.940 1.511 0.148
factor(P)1953    1.466 1.167 1.841 0.001
factor(P)1958    1.593 1.272 1.996 0.000

> round( ci.lin( m0, subset="P" ), 3 )

             Estimate StdErr      z      P  2.5% 97.5%
factor(P)1948    0.175  0.121  1.447 0.148 -0.062 0.413
factor(P)1953    0.382  0.116  3.286 0.001  0.154 0.610
factor(P)1958    0.466  0.115  4.052 0.000  0.241 0.691
```

Linear combinations of the parameters can be computed using the ctr.mat option:

```
> CM <- rbind( '1943 vs. 1953' = c( 0, -1, 0 ),
+             '1948 vs. 1953' = c( 1, -1, 0 ),
+             'Ref. (1953)' = c( 0, 0, 0 ),
+             '1958 vs. 1953' = c( 0, -1, 1 ) )
> round( ci.exp( m0, subset="P", ctr.mat=CM ), 3 )

             exp(Est.) 2.5% 97.5%
1943 vs. 1953    0.682 0.543 0.857
1948 vs. 1953    0.813 0.655 1.010
Ref. (1953)      1.000 1.000 1.000
1958 vs. 1953    1.087 0.887 1.332
```

## Age-Period and Age-Cohort models

### Bendix Carstensen

Statistical Analysis in the Lexis Diagram:

Age-Period-Cohort models

— and some cousins

European Doctoral School of Demography, Odense, June 2018

<http://BendixCarstensen/APC/EDSD-2018>

### Register data — rates

Rates in "tiles" of the Lexis diagram:

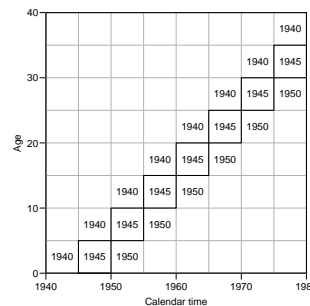
$$\lambda(a, p) = D_{ap} / Y_{ap}$$

Descriptive epidemiology based on disease registers:

How do the rates vary by age and time:

- Age-specific rates for a given period.
- Age-standardized rates as a function of calendar time. (Weighted averages of the age-specific rates).

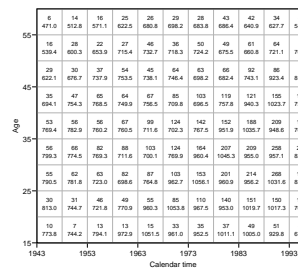
### "Synthetic" cohorts



Events and risk time in cells along the diagonals are among persons with roughly same date of birth.

Successively overlapping 10-year periods.

### Lexis diagram: data



Testis cancer cases in Denmark.

Male person-years in Denmark.



## Data matrix: Testis cancer cases

Number of cases

Age	Date of diagnosis ( <i>year</i> – 1900)								
	48–52	53–57	58–62	63–67	68–72	73–77	78–82	83–87	88–92
15–19	7	13	13	15	33	35	37	49	51
20–24	31	46	49	55	85	110	140	151	150
25–29	62	63	82	87	103	153	201	214	268
30–34	66	82	88	103	124	164	207	209	258
35–39	56	56	67	99	124	142	152	188	209
40–44	47	65	64	67	85	103	119	121	155
45–49	30	37	54	45	64	63	66	92	86
50–54	28	22	27	46	36	50	49	61	64
55–59	14	16	25	26	29	28	43	42	34

Age-Period and Age-Cohort models (AP-AC)

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

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

Age-Period and Age-Cohort models (AP-AC)

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## Data matrix: Male risk time

1000 person-years

Age	Date of diagnosis ( <i>year</i> – 1900)								
	48–52	53–57	58–62	63–67	68–72	73–77	78–82	83–87	88–92
15–19	744.2	794.1	972.9	1051.5	961.0	952.5	1011.1	1005.0	929.8
20–24	744.7	721.8	770.9	960.3	1053.8	967.5	953.0	1019.7	1017.3
25–29	781.8	723.0	698.6	764.8	962.7	1056.1	960.9	956.2	1031.6
30–34	774.5	769.3	711.6	700.1	769.9	960.4	1045.3	955.0	957.1
35–39	782.9	760.2	760.5	711.6	702.3	767.5	951.9	1035.7	948.6
40–44	754.3	768.5	749.9	756.5	709.8	696.5	757.8	940.3	1023.7
45–49	676.7	737.9	753.5	738.1	746.4	698.2	682.4	743.1	923.4
50–54	600.3	653.9	715.4	732.7	718.3	724.2	675.5	660.8	721.1
55–59	512.8	571.1	622.5	680.8	698.2	683.8	686.4	640.9	627.7

Age-Period and Age-Cohort models (AP-AC)

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```
> ts <- transform( subset( testisDK, A>14 & A<60 ),
+                 A = floor( A /5)*5 +2.5,
+                 P = floor((P-1943)/5)*5+1943+2.5 )
> ts$C <- ts$P - ts$A
> trate <- xtabs( D ~ A + P, data = ts ) /
+           xtabs( Y ~ A + P, data = ts ) * 100000
> #
> #
> #
> trate[1:5,1:6]
```

A	P	1945.5	1950.5	1955.5	1960.5	1965.5	1970.5
17.5	1.2923036	0.9405857	1.6370257	1.3362759	1.4264867	3.4340862	
22.5	3.6899378	4.1627194	6.3728682	6.3565492	5.7274822	8.0657826	
27.5	6.9576174	7.9301414	8.7140826	11.7375624	11.3753792	10.6996275	
32.5	7.0061961	8.5211703	10.6590661	12.3665762	14.7122260	16.1068525	
37.5	6.8888785	7.1529555	7.3663549	8.8105514	13.9126492	17.6571019	

Age-Period and Age-Cohort models (AP-AC)

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## Data matrix: Empirical rates

Rate per 1000,000 person-years

Age	Date of diagnosis ( <i>year</i> – 1900)								
	48–52	53–57	58–62	63–67	68–72	73–77	78–82	83–87	88–92
15–19	9.4	16.4	13.4	14.3	34.3	36.7	36.6	48.8	54.8
20–24	41.6	63.7	63.6	57.3	80.7	113.7	146.9	148.1	147.4
25–29	79.3	87.1	117.4	113.8	107.0	144.9	209.2	223.8	259.8
30–34	85.2	106.6	123.7	147.1	161.1	170.8	198.0	218.8	269.6
35–39	71.5	73.7	88.1	139.1	176.6	185.0	159.7	181.5	220.3
40–44	62.3	84.6	85.3	88.6	119.8	147.9	157.0	128.7	151.4
45–49	44.3	50.1	71.7	61.0	85.7	90.2	96.7	123.8	93.1
50–54	46.6	33.6	37.7	62.8	50.1	69.0	72.5	92.3	88.7
55–59	27.3	28.0	40.2	38.2	41.5	40.9	62.6	65.5	54.2

Age-Period and Age-Cohort models (AP-AC)

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```
> par( mfrow=c(2,2) )
> rateplot( trate, col=gray(2:15/18), lwd=3, ann=TRUE )
> wh = c("ap","ac","pa","ca")
> for( ptp in wh ) {
+   pdf( paste("./AP-AC-",ptp,".pdf",sep="" ), height=6, width=8 )
+   par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
+   rateplot( trate, which=ptp,
+            col=gray(2:15/18), lwd=3, ann=TRUE, a.lim=c(15,60) )
+   dev.off()
+ }
```

Age-Period and Age-Cohort models (AP-AC)

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## The classical plots

Given a table of rates classified by age and period, we can do 4 "classical" plots:

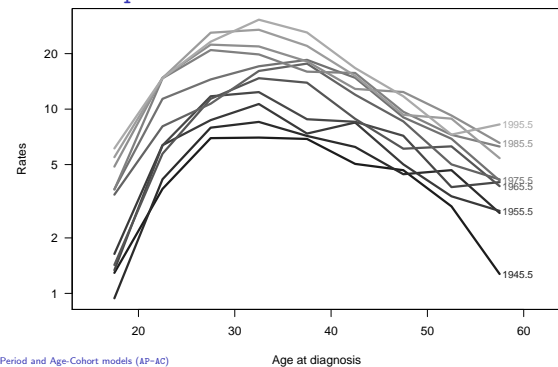
- ▶ Rates versus age at diagnosis (period):
  - rates in the same age-class connected.
- ▶ Rates versus age at diagnosis:
  - rates in the same birth-cohort connected.
- ▶ Rates versus date of diagnosis:
  - rates in the same ageclass connected.
- ▶ Rates versus date of date of birth:
  - rates in the same ageclass connected.

These plots can be produced by the R-function `rateplot`.

Age-Period and Age-Cohort models (AP-AC)

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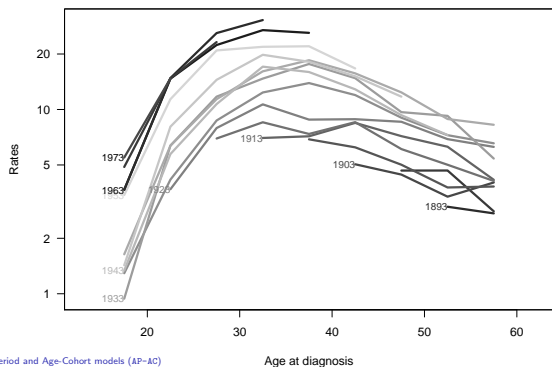
## which = "ap"



Age-Period and Age-Cohort models (AP-AC)

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which = "ac"



Age-Period and Age-Cohort models (AP-AC)

### Fitting the A-P model in R I

Reference period is the 5th period (1970.5 ~ 1968-72):

```
> ap <- glm( D ~ factor(A) - 1 + relevel( factor(P), "1970.5" ) +
+         offset( log(Y/10^5) ),
+         family=poisson, data=ts )
> summary( ap )

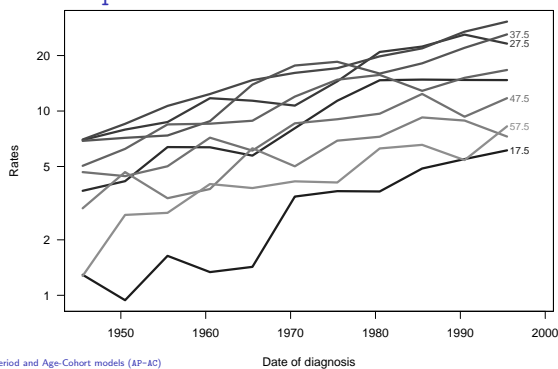
Call:
glm(formula = D ~ factor(A) - 1 + relevel(factor(P), "1970.5") +
    offset(log(Y/10^5)), family = poisson, data = ts)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-3.1850  -0.9465  -0.1683   0.5767   3.8610

Coefficients:
                                Estimate Std. Error z value Pr(>|z|)
```

Age-Period and Age-Cohort models (AP-AC)

which = "pa"



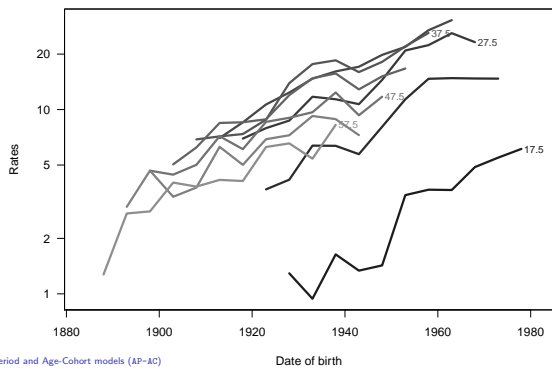
Age-Period and Age-Cohort models (AP-AC)

### Fitting the A-P model in R II

```
factor(A)17.5          1.06715    0.06791  15.715 < 2e-16
factor(A)22.5          2.20732    0.04837  45.630 < 2e-16
factor(A)27.5          2.65463    0.04465  59.449 < 2e-16
factor(A)32.5          2.77057    0.04458  62.142 < 2e-16
factor(A)37.5          2.63081    0.04606  57.122 < 2e-16
factor(A)42.5          2.36224    0.04878  48.422 < 2e-16
factor(A)47.5          2.01945    0.05341  37.811 < 2e-16
factor(A)52.5          1.73119    0.05957  29.062 < 2e-16
factor(A)57.5          1.45070    0.06748  21.498 < 2e-16
relevel(factor(P), "1970.5")1945.5 -0.75072    0.07011 -10.708 < 2e-16
relevel(factor(P), "1970.5")1950.5 -0.59740    0.06633  -9.006 < 2e-16
relevel(factor(P), "1970.5")1955.5 -0.43562    0.06299  -6.916 4.65e-12
relevel(factor(P), "1970.5")1960.5 -0.27952    0.05999  -4.659 3.18e-06
relevel(factor(P), "1970.5")1965.5 -0.16989    0.05751  -2.954 0.00313
relevel(factor(P), "1970.5")1975.5  0.16037    0.05143   3.118 0.00182
relevel(factor(P), "1970.5")1980.5  0.30022    0.04953   6.061 1.35e-09
relevel(factor(P), "1970.5")1985.5  0.37491    0.04853   7.726 1.11e-14
relevel(factor(P), "1970.5")1990.5  0.47047    0.04745   9.916 < 2e-16
relevel(factor(P), "1970.5")1995.5  0.54079    0.04862  11.123 < 2e-16
```

Age-Period and Age-Cohort models (AP-AC)

which = "ca"



Age-Period and Age-Cohort models (AP-AC)

### Fitting the A-P model in R III

```
(Dispersion parameter for poisson family taken to be 1)

Null deviance: 29193.6 on 2430 degrees of freedom
Residual deviance: 2816.6 on 2411 degrees of freedom
AIC: 9005

Number of Fisher Scoring iterations: 5
```

Age-Period and Age-Cohort models (AP-AC)

### Age-Period model

Rates are proportional between periods:

$$\lambda(a, p) = a_a \times b_p \quad \text{or} \quad \log[\lambda(a, p)] = \alpha_a + \beta_p$$

Choose  $p_0$  as reference period, where  $\beta_{p_0} = 0$

$$\log[\lambda(a, p_0)] = \alpha_a + \beta_{p_0} = \alpha_a$$

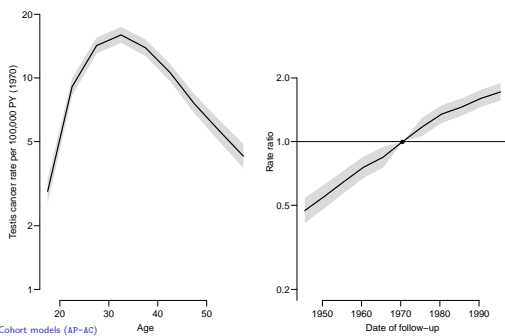
Age-Period and Age-Cohort models (AP-AC)

### Estimates with confidence intervals

```
> par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
> matshade( seq(17.5,57.5,5), ci.exp(ap,subset="A"), plot=TRUE,
+         log="y", lwd=2, ylim=c(1,20), xlab="Age",
+         ylab="Testis cancer rate per 100,000 PY (1970)" )
> matshade( seq(1945.5,1995.5,5),
+         rbind( ci.exp(ap,subset="P")[1:5,], 1,
+               ci.exp(ap,subset="P")[6:10,] ), plot=TRUE,
+         log="y", lwd=2, ylim=c(1,20)/5,
+         xlab="Date of follow-up", ylab="Rate ratio" )
> abline( h = 1 )
> points( 1970.5, 1, pch=16 )
```

Age-Period and Age-Cohort models (AP-AC)

## Estimates from Age-Period model



Age-Period and Age-Cohort models (AP-AC)

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## Fitting the A-C model in R III

```
relevel(factor(C), "1933")1948 0.18088 0.05256 3.441 0.000579
relevel(factor(C), "1933")1953 0.42239 0.05309 7.956 1.77e-15
relevel(factor(C), "1933")1958 0.62544 0.05421 11.537 < 2e-16
relevel(factor(C), "1933")1963 0.75687 0.05727 13.215 < 2e-16
relevel(factor(C), "1933")1968 0.75183 0.06799 11.057 < 2e-16
relevel(factor(C), "1933")1973 0.87343 0.09373 9.318 < 2e-16
relevel(factor(C), "1933")1978 1.19601 0.17340 6.898 5.29e-12
```

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 29193.6 on 2430 degrees of freedom  
Residual deviance: 2767.8 on 2403 degrees of freedom  
AIC: 8972.2

Number of Fisher Scoring iterations: 5

Age-Period and Age-Cohort models (AP-AC)

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## Age-cohort model

Rates are proportional between cohorts:

$$\lambda(a, c) = a_a \times c_c \quad \text{or} \quad \log[\lambda(a, p)] = \alpha_a + \gamma_c$$

Choose  $c_0$  as reference cohort, where  $\gamma_{c_0} = 0$

$$\log[\lambda(a, c_0)] = \alpha_a + \gamma_{c_0} = \alpha_a$$

Age-Period and Age-Cohort models (AP-AC)

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## Estimates with confidence intervals

```
> par( mfrow=c(1,2), mar=c(3,3,1,1), mgp=c(3,1,0)/1.6, bty="n", las=1 )
> matshade( seq(17.5,57.5,5), ci.exp(ac,subset="A"), plot=TRUE,
+ log="y", lwd=2, ylim=c(1,20), xlab="Age",
+ ylab="Testis cancer rate per 100,000 PY (1933 cohort)" )
> matshade( seq(1888,1978,5),
+ rbind( ci.exp(ac,subset="C")[1:9, ], 1,
+ ci.exp(ac,subset="C")[10:18, ] ), plot=TRUE,
+ log="y", lwd=2, ylim=c(1,20)/5,
+ xlab="Date of birth", ylab="Rate ratio" )
> abline( h = 1 )
> points( 1933, 1, pch=16 )
```

Age-Period and Age-Cohort models (AP-AC)

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## Fitting the A-C model in R I

Reference period is the 1933 cohort:

```
> ac <- glm( D ~ factor(A) - 1 + relevel( factor(C), "1933" ) +
+ offset( log(Y/10^5) ),
+ family=poisson, data=ts )
> summary( ac )
```

Call:  
glm(formula = D ~ factor(A) - 1 + relevel(factor(C), "1933") +  
offset(log(Y/10^5)), family = poisson, data = ts)

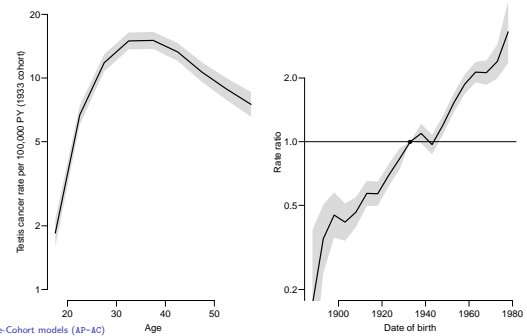
Deviance Residuals:  
Min 1Q Median 3Q Max  
-3.0796 -0.9538 -0.1620 0.5767 3.9525

Coefficients:  
factor(A)17.5 Estimate Std. Error z value Pr(>|z|)  
0.61513 0.07534 8.165 3.23e-16

Age-Period and Age-Cohort models (AP-AC)

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## Estimates from Age-Cohort model



Age-Period and Age-Cohort models (AP-AC)

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## Fitting the A-C model in R II

```
factor(A)22.5 1.89965 0.05342 35.558 < 2e-16
factor(A)27.5 2.46911 0.04842 50.990 < 2e-16
factor(A)32.5 2.70635 0.04695 57.639 < 2e-16
factor(A)37.5 2.71211 0.04758 57.006 < 2e-16
factor(A)42.5 2.58676 0.04993 51.803 < 2e-16
factor(A)47.5 2.36542 0.05459 43.327 < 2e-16
factor(A)52.5 2.18192 0.06098 35.782 < 2e-16
factor(A)57.5 2.01519 0.06939 29.041 < 2e-16
relevel(factor(C), "1933")1888 -1.77316 0.41400 -4.283 1.84e-05
relevel(factor(C), "1933")1893 -1.05641 0.19017 -5.555 2.77e-08
relevel(factor(C), "1933")1898 -0.79897 0.12600 -6.341 2.28e-10
relevel(factor(C), "1933")1903 -0.87599 0.10389 -8.432 < 2e-16
relevel(factor(C), "1933")1908 -0.76707 0.08352 -9.184 < 2e-16
relevel(factor(C), "1933")1913 -0.56290 0.07006 -8.035 9.36e-16
relevel(factor(C), "1933")1918 -0.56702 0.06683 -8.484 < 2e-16
relevel(factor(C), "1933")1923 -0.36836 0.06124 -6.015 1.79e-09
relevel(factor(C), "1933")1928 -0.18832 0.05903 -3.190 0.001421
relevel(factor(C), "1933")1938 0.08958 0.05439 1.647 0.099585
relevel(factor(C), "1933")1943 -0.03107 0.05443 -0.571 0.568091
```

Age-Period and Age-Cohort models (AP-AC)

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## Recap of Monday — rates

- ▶ Rate, intensity:  $\lambda(t) = P\{\text{event in } (t, t+h) \mid \text{alive at } t\} / h$
- ▶ Observe empirical rates  $(d, y)$  — possibly many per person.
- ▶  $\ell_{FU} = d \log(\lambda) - \lambda y$ , obs:  $(d, y)$ , rate par:  $\lambda$
- ▶  $\ell_{Poisson} = d \log(\lambda y) - \lambda y$ , obs:  $d$ , mean par:  $\mu = \lambda y$
- ▶  $\ell_{Poisson} - \ell_{FU} = d \log(y)$  does not involve  $\lambda$   
— use either to find m.l.e. of  $\lambda$
- ▶ Poisson model is for  $\log(\mu) = \log(\lambda y) = \log(\lambda) + \log(y)$   
hence  $\text{offset} = \log(Y)$
- ▶ Once rates are known, we can construct survival curves and derivatives of that.

Age-Period and Age-Cohort models (AP-AC)

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## Recap Monday — models

- Empirical rate ( $d_t, y_t$ ) relates to a **time**  $t$
- Many for the same person — different times
- Not independent, but likelihood is a product
- One parameter per interval  $\Rightarrow$  exchangeable times
- Use the quantitative nature of  $t$ :  $\Rightarrow$  smooth continuous effects of time
- Predicted rates: `ci.pred( model, newdata=nd )`
- RR is the difference between two predictions:
- RR by period:
- `ndx<-data.frame(P=1947:1980,A=47)`
- `ndr<-data.frame(P=1870,A=47)`
- `ci.exp( model, ctr.mat=list(ndx-ndr))`

## Age and linear effect of cohort:

```
> acd <- glm( D ~ factor( A ) - 1 + I(C-1933) +
+           offset( log( Y ) ),
+           family=poisson )
> summary( acd )

Call:
glm(formula = D ~ factor(A) - 1 + I(C - 1933) + offset(log(Y)), family = poisson)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.97593  -0.77091   0.02809   0.95914   2.93076

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
factor(A)17.5  -4.11117    0.06760  -60.82  <2e-16
...
factor(A)57.5  -2.64527    0.06423  -41.19  <2e-16
I(C - 1933)    0.02653    0.00100   26.52  <2e-16

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 89358.53 on 81 degrees of freedom
Residual deviance: 126.07 on 71 degrees of freedom
```

## Age-drift model

### Bendix Carstensen

Statistical Analysis in the  
Lexis Diagram:

Age-Period-Cohort models  
— and some cousins

European Doctoral School of Demography, Odense,  
June 2018

<http://BendixCarstensen/APC/EDSD-2018>

## What goes on?

$$p = a + c \quad p_0 = a_0 + c_0$$

$$\begin{aligned} \alpha_a + \beta(p - p_0) &= \alpha_a + \beta(a + c - (a_0 + c_0)) \\ &= \underbrace{\alpha_a + \beta(a - a_0)}_{\text{cohort age-effect}} + \beta(c - c_0) \end{aligned}$$

The two **models** are the same.

The **parametrization** is different.

The age-curve refers either

- to a period (cross-sectional rates) or
- to a cohort (longitudinal rates).

## Linear effect of period:

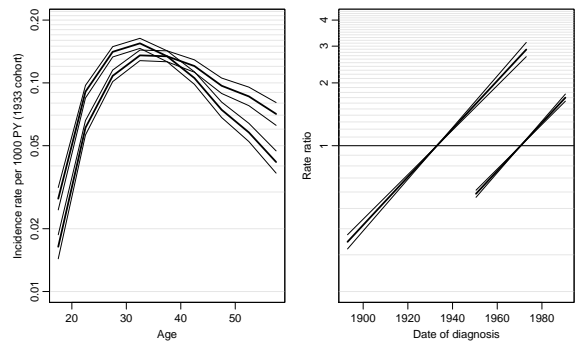
$$\log[\lambda(a, p)] = \alpha_a + \beta_p = \alpha_a + \beta(p - p_0)$$

that is,  $\beta_p = \beta(p - p_0)$ .

## Linear effect of cohort:

$$\log[\lambda(a, p)] = \tilde{\alpha}_a + \gamma_c = \tilde{\alpha}_a + \gamma(c - c_0)$$

that is,  $\gamma_c = \gamma(c - c_0)$



Which age-curve is period and which is cohort?

## Age and linear effect of period:

```
> apd <- glm( D ~ factor( A ) - 1 + I(P-1970.5) +
+           offset( log( Y ) ),
+           family=poisson )
> summary( apd )
```

```
Call:
glm(formula = D ~ factor(A) - 1 + I(P - 1970.5) + offset(log(Y)), family = poisson)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.97593  -0.77091   0.02809   0.95914   2.93076
```

```
Coefficients:
            Estimate Std. Error z value Pr(>|z|)
factor(A)17.5  -3.58065    0.06306  -56.79  <2e-16
...
factor(A)57.5  -3.17579    0.06256  -50.77  <2e-16
I(P - 1970.5)  0.02653    0.00100   26.52  <2e-16
```

(Dispersion parameter for poisson family taken to be 1)

```
Null deviance: 89358.53 on 81 degrees of freedom
Residual deviance: 126.07 on 71 degrees of freedom
```

## Age-Period-Cohort model

### Bendix Carstensen

Statistical Analysis in the  
Lexis Diagram:

Age-Period-Cohort models

— and some cousins

European Doctoral School of Demography, Odense,  
June 2018

<http://BendixCarstensen/APC/EDSD-2018>

## The age-period-cohort model

$$\log[\lambda(a, p)] = \alpha_a + \beta_p + \gamma_c$$

- ▶ Three effects:
  - ▶  $a$  — Age (at diagnosis)
  - ▶  $p$  — Period (of diagnosis)
  - ▶  $c$  — Cohort (of birth)
- ▶ No assumptions about the **shape** of effects.
- ▶ Levels of A, P and C are assumed **exchangeable**
- ▶ *i.e.* no assumptions about the relationship between parameter estimates and the **scaled values** of A, P and C

## Fitting the model in R IV

```
factor(C)1923 0.03280 0.25971 0.126 0.89950
factor(C)1928 0.02155 0.23945 0.090 0.92830
factor(C)1933 0.02518 0.21988 0.115 0.90881
factor(C)1938 -0.07240 0.20268 -0.357 0.72094
factor(C)1943 -0.35284 0.18706 -1.886 0.05927
factor(C)1948 -0.30472 0.17308 -1.761 0.07831
factor(C)1953 -0.17916 0.16258 -1.102 0.27047
factor(C)1958 -0.11739 0.15585 -0.753 0.45133
factor(C)1963 -0.10882 0.15410 -0.706 0.48008
factor(C)1968 -0.16807 0.16235 -1.035 0.30053
factor(C)1973 NA NA NA NA
```

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 2761.230 on 89 degrees of freedom  
Residual deviance: 38.783 on 56 degrees of freedom  
AIC: 637.64

Number of Fisher Scoring iterations: 4

## Fitting the model in R I

```
> library( Epi )
> data( testisDK )
> tc <- transform( subset( testisDK, A>14 & A<60 & P<1993 ),
+                 A = floor( A /5)*5 +2.5,
+                 P = floor((P-1943)/5)*5+1943+2.5 )
> tc <- aggregate( tc[,c("D","Y")], tc[,c("A","P")], FUN=sum )
> tc$C <- tc$P - tc$A
> str( tc )

'data.frame': 90 obs. of 5 variables:
 $ A: num 17.5 22.5 27.5 32.5 37.5 42.5 47.5 52.5 57.5 17.5 ...
 $ P: num 1946 1946 1946 1946 1946 ...
 $ D: num 10 30 55 56 53 35 29 16 6 7 ...
 $ Y: num 773812 813022 790500 799293 769356 ...
 $ C: num 1928 1923 1918 1913 1908 ...
```

## Fitting the model in R V

## Fitting the model in R II

```
> m.apc <- glm( D ~ factor(A) + factor(P) + factor(C) + offset(log(Y)),
+             family = poisson, data = tc )
> summary( m.apc )

Call:
glm(formula = D ~ factor(A) + factor(P) + factor(C) + offset(log(Y)),
    family = poisson, data = tc)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.5406  -0.5534   0.0000   0.4934   1.2966

Coefficients: (1 not defined because of singularities)
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  -11.39890     0.23316  -48.889 < 2e-16
factor(A)22.5  1.19668     0.07789  15.364 < 2e-16
factor(A)27.5  1.63551     0.08627  18.957 < 2e-16
factor(A)32.5  1.71939     0.10223  16.819 < 2e-16
factor(A)37.5  1.57062     0.12205  12.869 < 2e-16
```

## No. of parameters

A has  $9(A)$  levels

P has  $10(P)$  levels

C=P-A has  $18(C = A + P - 1)$  levels

Age-drift model has  $A + 1 = 10$  parameters

Age-period model has  $A + P - 1 = 18$  parameters

Age-cohort model has  $A + C - 1 = 26$  parameters

Age-period-cohort model has  $A + P + C - 3 = 34$  parameters:

```
> length( coef(m.apc) ) ; sum( !is.na(coef(m.apc)) )
[1] 35
[1] 34
```

The missing parameter is because of the **identifiability problem**.

## Fitting the model in R III

```
factor(A)42.5 1.29418 0.14416 8.977 < 2e-16
factor(A)47.5 0.87209 0.16828 5.182 2.19e-07
factor(A)52.5 0.51257 0.19309 2.655 0.00794
factor(A)57.5 0.12801 0.21109 0.606 0.54424
factor(P)1950.5 0.20286 0.08247 2.460 0.01390
factor(P)1955.5 0.42044 0.09081 4.630 3.66e-06
factor(P)1960.5 0.64099 0.10548 6.077 1.23e-09
factor(P)1965.5 0.82135 0.12407 6.620 3.60e-11
factor(P)1970.5 1.06435 0.14444 7.369 1.72e-13
factor(P)1975.5 1.27796 0.16653 7.674 1.67e-14
factor(P)1980.5 1.43441 0.18961 7.565 3.88e-14
factor(P)1985.5 1.50578 0.21339 7.056 1.71e-12
factor(P)1990.5 1.58798 0.23562 6.740 1.59e-11
factor(C)1893 0.50556 0.42894 1.179 0.23855
factor(C)1898 0.56443 0.38398 1.470 0.14158
factor(C)1903 0.28430 0.35557 0.800 0.42397
factor(C)1908 0.20683 0.32836 0.630 0.52877
factor(C)1913 0.22302 0.30344 0.735 0.46236
factor(C)1918 0.02713 0.28150 0.096 0.92322
```

## Test for effects

```
> tc.acp <- apc.fit( tc, model="factor", ref.c=1943, scale=10^5 )
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

            Resid. Df Resid. Dev  Df Deviance  Pr(>Chi)
Age                81    1114.65
Age-drift          80    131.77  1  982.88 < 2.2e-16
Age-Cohort         64    70.20  16  61.57 2.84e-07
Age-Period-Cohort  56    38.78  8   31.42 0.0001183
Age-Period         72    122.23 -16  -83.45 3.95e-11
Age-drift          80    131.77  -8   -9.54 0.2989863
```

## How to choose a parametrization

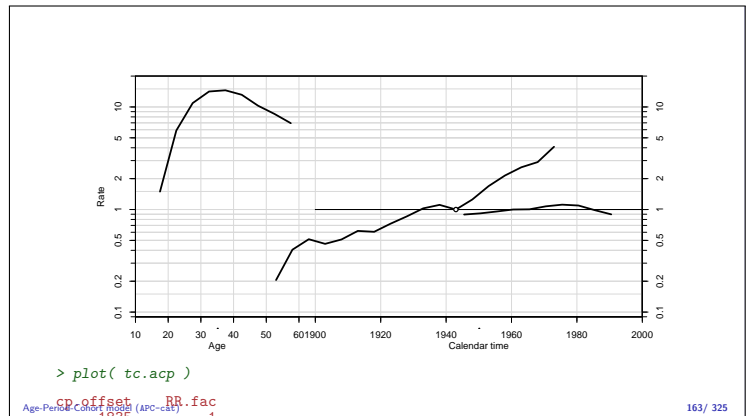
- ▶ Standard approach: Put extremes of periods or cohorts to 0, and choose a reference for the other.
- ▶ Clayton & Schifflers: only 2nd order differences are invariants:

$$\alpha_{i-1} - 2\alpha_i + \alpha_{i+1}$$

Implemented in Epi via the contrast type `contr.2nd` (later).

- ▶ Holford: Extract linear effects by regression:

$$\lambda(a, p) = \hat{\alpha}_a + \hat{\beta}_p + \hat{\gamma}_c = \tilde{\alpha}_a + \tilde{\beta}_p + \tilde{\gamma}_c + \hat{\mu}_a + \hat{\mu}_p + \hat{\mu}_c + \hat{\delta}_a a + \hat{\delta}_p p + \hat{\delta}_c c$$



## Assumptions

Assumptions are needed to do this, e.g.:

- ▶ Age is the major time scale
- ▶ Cohort is the secondary time scale (the major secular trend)
- ▶  $c_0$  is the reference cohort
- ▶ Period is the residual time scale: 0 on average, 0 slope
- ▶ ... constraining first and last period parameter to 0 is a crude way of obtaining this.

Customize the frame for nicer plot of parameter estimates:

```
> par( mar=c(3,4,0.1,4), mgp=c(3,1,0)/1.6, las=1 )
> apc.frame( a.lab=c(2,4,6)*10,
+           a.tic=1:6*10,
+           cp.lab=1900+0:4*20,
+           cp.tic=1890+0:10*10,
+           r.lab=c(c(1,2,5),c(1,2)*10),
+           r.tic=c(1:10,15,20,25),
+           rr.ref=5 )
> matshade( tc.acp$Age[,1], tc.acp$Age[,-1], lwd=2 )
> pc.matshade( tc.acp$Per[,1], tc.acp$Per[,-1], lwd=2 )
> pc.matshade( tc.acp$Coh[,1], tc.acp$Coh[,-1], lwd=2 )
> pc.points( 1943, 1, pch=16 )
```

## Relocating effects between A, P and C

Period effect, 0 on average, slope is 0: a regression of  $\beta_p$  on  $p$ :

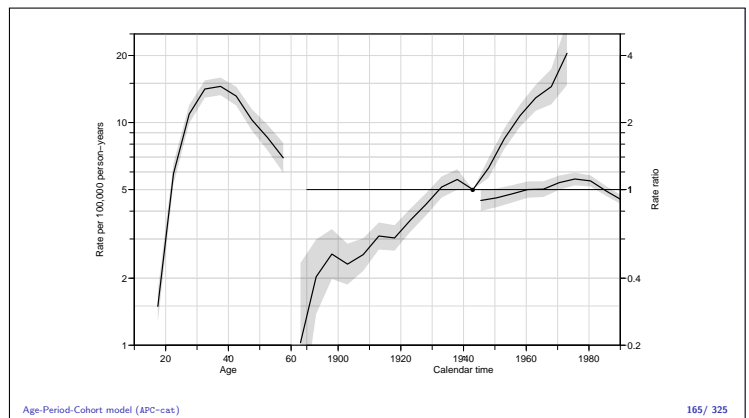
$$g(p) = \tilde{\beta}_p = \beta_p - \hat{\mu}_p - \hat{\delta}_p p$$

Cohort effect, absorbing all time-trend ( $\delta_p p = \delta_p(a + c)$ ) and risk relative to  $c_0$ :

$$h(c) = \gamma_c - \gamma_{c_0} + \hat{\delta}_p(c - c_0)$$

The rest is the age-effect:

$$f(a) = \alpha_a + \hat{\mu}_p + \hat{\delta}_p a + \hat{\delta}_p c_0 + \gamma_{c_0}$$



## How it all adds up:

$$\begin{aligned} \lambda(a, p) &= \hat{\alpha}_a + \hat{\beta}_p + \hat{\gamma}_c \\ &= \hat{\alpha}_a + \gamma_{c_0} + \hat{\mu}_p + \hat{\delta}_p(a + c_0) + \\ &\quad \hat{\beta}_p - \hat{\mu}_p - \hat{\delta}_p(a + c) + \\ &\quad \hat{\gamma}_c - \gamma_{c_0} + \hat{\delta}_p(c - c_0) \end{aligned}$$

Only the regression on period is needed! (For this model...)

## A simple practical approach

- ▶ First fit the age-cohort model, with cohort  $c_0$  as reference and get estimates  $\hat{\alpha}_a$  and  $\hat{\gamma}_c$ :

$$\log[\lambda(a, p)] = \hat{\alpha}_a + \hat{\gamma}_c$$

- ▶ Then consider the full APC-model with age and cohort effects constrained to be as estimated from the AC-model:

$$\log[\lambda(a, p)] = \hat{\alpha}_a + \hat{\gamma}_c + \beta_p$$

- ▶ The residual period effect can be estimated if we note that for the number of cases we have:

$$\log(\text{expected cases}) = \log[\hat{\lambda}(a, p) Y] = \underbrace{\hat{\alpha}_a + \hat{\gamma}_c + \log(Y)}_{\text{"known"}} + \beta_p$$

- ▶ This is analogous to the expression for a Poisson model in general,
- ▶ ... but now is the offset not just  $\log(Y)$  but  $\hat{\alpha}_a + \hat{\gamma}_c + \log(Y)$ , the log of the fitted values from the age-cohort model.
- ▶  $\beta_p$  are estimated in a Poisson model with this as offset.
- ▶ Advantage: We get the standard errors for free.

## Age at entry Age-Duration-Diagnosis

Bendix Carstensen

Statistical Analysis in the  
Lexis Diagram:

Age-Period-Cohort models

— and some cousins

European Doctoral School of Demography, Odense,  
June 2018

<http://BendixCarstensen/APC/EDSD-2018>

Customize the frame for nicer plot of parameter estimates:

```
> par( mar=c(3,4,0.1,4), mgp=c(3,1,0)/1.6, las=1 )
> apc.frame( a.lab=c(2,4,6)*10,
+          a.tic=1:6*10,
+          cp.lab=1900+0:4*20,
+          cp.tic=1890+0:10*10,
+          r.lab=c(c(1,2,5),c(1,2)*10),
+          r.tic=c(1:10,15,20,25),
+          rr.ref=5 )
> matshade( tc.acp$Age[,1], tc.acp$Age[,-1], lwd=2, alpha=0.2 )
> pc.matshade( tc.acp$Per[,1], tc.acp$Per[,-1], lwd=2, alpha=0.2 )
> pc.matshade( tc.acp$Coh[,1], tc.acp$Coh[,-1], lwd=2, alpha=0.2 )
> pc.points( 1943, 1, pch=16 )
> #
> # The stepwise conditioning:
> tc.ac.p <- apc.fit( tc, model="factor", parm="AC-P", ref.c=1943, scale=10^5 )
```

## Age at entry (diagnosis) as covariate

$t$ : time since entry (duration)

$e$ : age at entry

$a = e + t$ : current age (age at follow-up)

Duration as basic time-scale; linear effect of age at entry:

$$\log(\lambda(a, t)) = f(t) + \beta e = (f(t) - \beta t) + \beta a$$

Immaterial whether  $a$  or  $e$  is used as (log)-linear covariate as long as  $t$  is in the model.

[1] "Sequential modelling Poisson with log(Y) offset : ( AC-P ):\n"

Analysis of deviance for Age-Period-Cohort model

	Resid. Df	Resid. Dev	Df	Deviance	Pr(>Chi)
Age	81	1114.65			
Age-drift	80	131.77	1	982.88	< 2.2e-16
Age-Cohort	64	70.20	16	61.57	2.84e-07
Age-Period-Cohort	56	38.78	8	31.42	0.0001183
Age-Period	72	122.23	-16	-83.45	3.95e-11
Age-drift	80	131.77	-8	-9.54	0.2989863

```
> #
> matshade( tc.ac.p$Age[,1], tc.ac.p$Age[,-1], lwd=2, alpha=0.2, lty='22', lend)
> pc.matshade( tc.ac.p$Per[,1], tc.ac.p$Per[,-1], lwd=2, alpha=0.2, lty='22', lend)
> pc.matshade( tc.ac.p$Coh[,1], tc.ac.p$Coh[,-1], lwd=2, alpha=0.2, lty='22', lend)
```

## Non-linear effects of time-scales

Arbitrary effects of the three variables  $t$ ,  $a$  and  $e$ :

⇒ genuine extension of the model.

$$\log(\lambda(a, t)) = f(t) + g(a) + h(e)$$

Three quantities can be arbitrarily moved between the three functions:

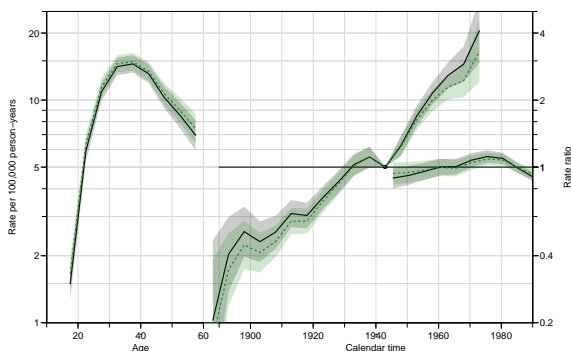
$$\tilde{f}(t) = f(t) - \mu_a - \mu_e + \gamma t$$

$$\tilde{g}(a) = g(a) + \mu_a - \gamma a$$

$$\tilde{h}(e) = h(e) + \mu_a + \gamma e$$

because  $t - a + e = 0$ .

This is the age-period-cohort modelling problem again.



## "Controlling for age"

— is not a well defined statement:

- ▶ Mostly it means that age **at entry** is included in the model.
- ▶ But ideally one would check whether there were non-linear effects of age at entry and current age.
- ▶ This would require modelling of multiple timescales.
- ▶ Which is best accomplished by splitting follow up and using Poisson models, with time scales as covariates.

# Tabulation in the Lexis diagram

Bendix Carstensen

Statistical Analysis in the Lexis Diagram:

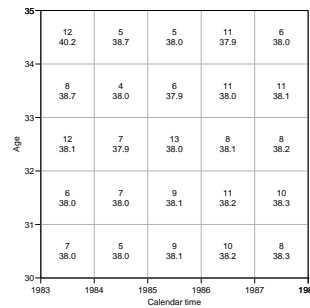
Age-Period-Cohort models  
— and some cousins

European Doctoral School of Demography, Odense,  
June 2018

<http://BendixCarstensen/APC/EDSD-2018>

Lexis-tab

## Tabulation of register data

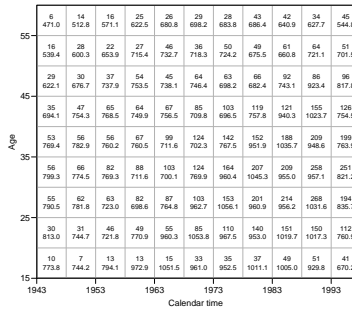


Testis cancer cases in Denmark.

Male person-years in Denmark.

Tabulation in the Lexis diagram (Lexis-tab)

## Tabulation of register data

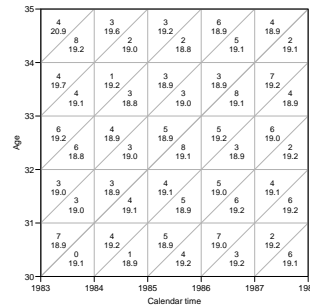


Testis cancer cases in Denmark.

Male person-years in Denmark.

Tabulation in the Lexis diagram (Lexis-tab)

## Tabulation of register data



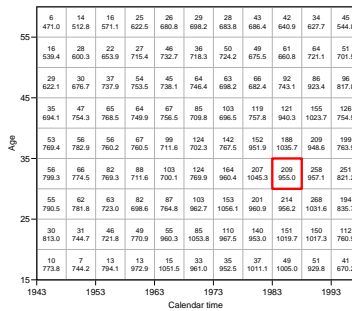
Testis cancer cases in Denmark.

Male person-years in Denmark.

Subdivision by year of birth (cohort).

Tabulation in the Lexis diagram (Lexis-tab)

## Tabulation of register data



Testis cancer cases in Denmark.

Male person-years in Denmark.

Tabulation in the Lexis diagram (Lexis-tab)

## Major sets in the Lexis diagram

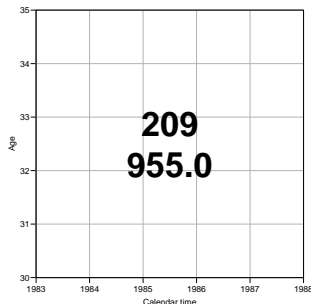
- A-sets: Classification by age and period. (□)
- B-sets: Classification by age and cohort. (▧)
- C-sets: Classification by cohort and period. (▨)

The mean age, period and cohort for these sets is just the mean of the tabulation interval.

The mean of the third variable is found by using  $a = p - c$ .

Tabulation in the Lexis diagram (Lexis-tab)

## Tabulation of register data



Testis cancer cases in Denmark.

Male person-years in Denmark.

Tabulation in the Lexis diagram (Lexis-tab)

Analysis of rates from a complete observation in a Lexis diagram need not be restricted to these classical sets classified by two factors.

We may classify cases and risk time by all three factors

**Lexis triangles:**

- Upper triangles: Classification by age and period, earliest born cohort. (▽)
- Lower triangles: Classification by age and period, latest born cohort. (▹)

Tabulation in the Lexis diagram (Lexis-tab)

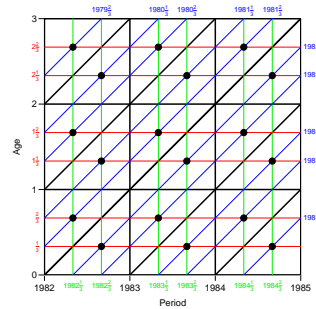


### Mean $a$ , $p$ and $c$ during FU in triangles

Modelling requires that each set (=observation in the dataset) be assigned a value of age, period and cohort. So for each triangle we need:

- ▶ mean age at risk.
- ▶ mean date at risk.
- ▶ mean cohort at risk.

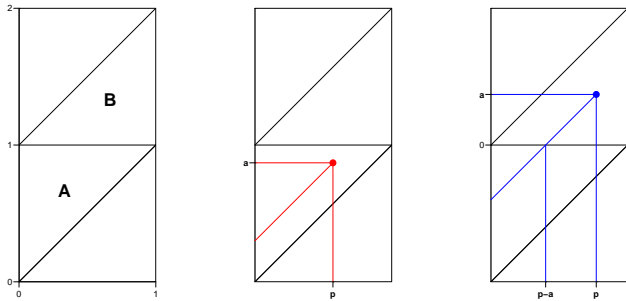
### Tabulation by age, period and cohort



Gives triangular sets with differing mean age, period and cohort:

These correct midpoints for age, period and cohort must be used in modelling.

### Means in upper (A) and lower (B) triangles:

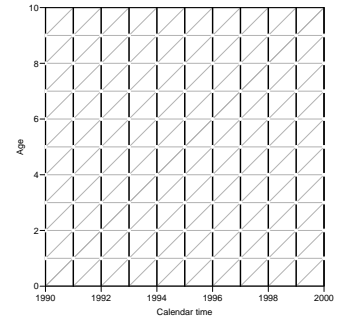


### From population figures to risk time

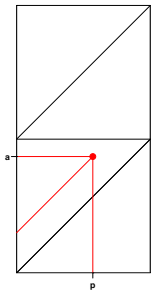
Population figures in the form of size of the population at certain date are available from most statistical bureaus.

This corresponds to population sizes along the vertical lines in the diagram.

We want risk time figures for the population in the squares and triangles in the diagram.



### Upper triangles ( $\nabla$ ), A:



$$E_{\mathbf{A}}(a) = \int_{p=0}^{p=1} \int_{a=p}^{a=1} a \times 2 \, da \, dp = \int_{p=0}^{p=1} 1 - p^2 \, dp = \frac{2}{3}$$

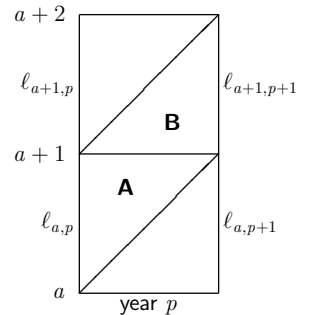
$$E_{\mathbf{A}}(p) = \int_{a=0}^{a=1} \int_{p=0}^{p=a} p \times 2 \, dp \, da = \int_{a=0}^{a=1} a^2 \, dp = \frac{1}{3}$$

$$E_{\mathbf{A}}(c) = \frac{1}{3} - \frac{2}{3} = -\frac{1}{3}$$

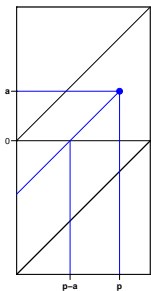
### Prevalent population figures

$\ell_{a,p}$  is the number of persons in age class  $a$  alive at the beginning of period (=year)  $p$ .

The aim is to compute person-years for the triangles **A** and **B**, respectively.



### Lower triangles ( $\triangle$ ), B:



$$E_{\mathbf{B}}(a) = \int_{p=0}^{p=1} \int_{a=0}^{a=p} a \times 2 \, da \, dp = \int_{p=0}^{p=1} p^2 \, dp = \frac{1}{3}$$

$$E_{\mathbf{B}}(p) = \int_{a=0}^{a=1} \int_{p=a}^{p=1} p \times 2 \, dp \, da = \int_{a=0}^{a=1} 1 - a^2 \, dp = \frac{2}{3}$$

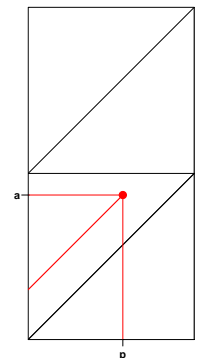
$$E_{\mathbf{B}}(c) = \frac{2}{3} - \frac{1}{3} = \frac{1}{3}$$

The area of the triangle is  $1/2$ , so the uniform measure over the triangle has density 2. Therefore a person dying in age  $a$  at date  $p$  in **A** contributes  $p$  risk time in **A**, so the average will be:

$$\int_{p=0}^{p=1} \int_{a=p}^{a=1} 2p \, da \, dp$$

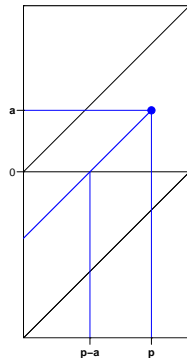
$$= \int_{p=0}^{p=1} 2p - 2p^2 \, dp$$

$$= \left[ p^2 - \frac{2p^3}{3} \right]_{p=0}^{p=1} = \frac{1}{3}$$



A person dying in age  $a$  at date  $p$  in **B** contributes  $p - a$  risk time in **A**, so the average will be (again using the density 2 of the uniform measure):

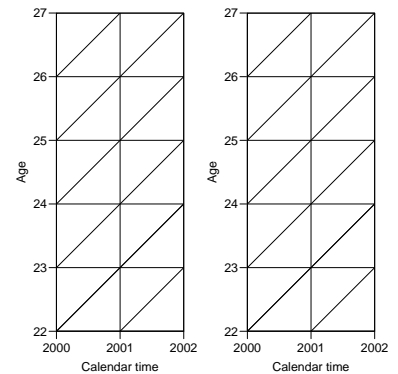
$$\begin{aligned} & \int_{p=0}^{p=1} \int_{a=0}^{a=p} 2(p-a) da dp \\ &= \int_{p=0}^{p=1} [2pa - a^2]_{a=0}^{a=p} dp \\ &= \int_{p=0}^{p=1} p^2 dp = \frac{1}{3} \end{aligned}$$



**Exercise:**

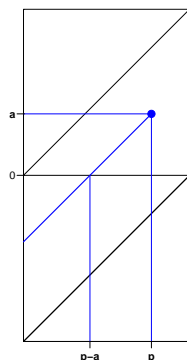
Fill in the risk time figures in as many triangles as possible from the previous table for men and women, respectively.

Look at the N2Y function in Ep1.



A person dying in age  $a$  at date  $p$  in **B** contributes  $a$  risk time in **B**, so the average will be:

$$\begin{aligned} & \int_{p=0}^{p=1} \int_{a=0}^{a=p} 2a da dp \\ &= \int_{p=0}^{p=1} p^2 dp = \frac{1}{3} \end{aligned}$$



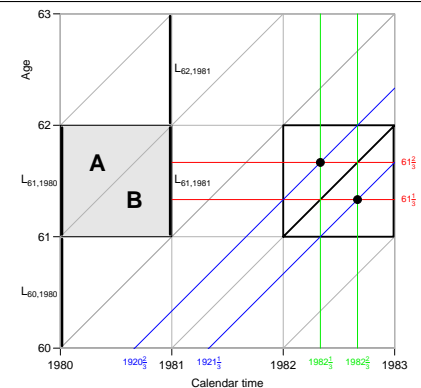
**Summary:**

Population risk time:

**A:**  $(\frac{1}{3}\ell_{a,p} + \frac{1}{6}\ell_{a+1,p+1}) \times 1y$

**B:**  $(\frac{1}{6}\ell_{a-1,p} + \frac{1}{3}\ell_{a,p+1}) \times 1y$

Mean age, period and cohort:  $\frac{1}{3}$  into the interval.



**Mean contributions to risk time in A and B:**

	<b>A:</b>	<b>B:</b>
Survivors:	$\ell_{a+1,p+1} \times \frac{1}{2}y$	$\ell_{a+1,p+1} \times \frac{1}{2}y$
Dead in <b>A:</b>	$\frac{1}{2}(\ell_{a,p} - \ell_{a+1,p+1}) \times \frac{1}{3}y$	
Dead in <b>B:</b>	$\frac{1}{2}(\ell_{a,p} - \ell_{a+1,p+1}) \times \frac{1}{3}y$	$\frac{1}{2}(\ell_{a,p} - \ell_{a+1,p+1}) \times \frac{1}{3}y$
$\Sigma$	$(\frac{1}{3}\ell_{a,p} + \frac{1}{6}\ell_{a+1,p+1}) \times 1y$	$(\frac{1}{6}\ell_{a,p} + \frac{1}{3}\ell_{a+1,p+1}) \times 1y$

The number of deaths in **A** and **B** is  $\ell_{a,p} - \ell_{a+1,p+1}$ , and we assume that half occur in **A** and half in **B**.

**APC-model for triangular data**

**Bendix Carstensen**

Statistical Analysis in the Lexis Diagram:

Age-Period-Cohort models — and some cousins

European Doctoral School of Demography, Odense, June 2018

<http://BendixCarstensen/APC/EDSD-2018>

Population as of 1. January from Statistics Denmark:

Age	Men			Women		
	2000	2001	2002	2000	2001	2002
22	33435	33540	32272	32637	32802	31709
23	35357	33579	33742	34163	32853	33156
24	38199	35400	33674	37803	34353	33070
25	37958	38257	35499	37318	37955	34526
26	38194	38048	38341	37292	37371	38119
27	39891	38221	38082	39273	37403	37525

**Model for triangular data**

- ▶ One parameter per distinct value on each timescale.
- ▶ Example: 3 age-classes and 3 periods:
  - ▶ 6 age parameters
  - ▶ 6 period parameters
  - ▶ 10 cohort parameters
- ▶ Model:

$$\lambda_{ap} = \alpha_a + \beta_p + \gamma_c$$

### Problem: Disconnected design!

Log-likelihood contribution from one triangle:

$$D_{ap} \log(\lambda_{ap}) - \lambda_{ap} Y_{ap} = D_{ap} \log(\alpha_a + \beta_p + \gamma_c) - (\alpha_a + \beta_p + \gamma_c) Y_{ap}$$

The log-likelihood can be separated:

$$\sum_{a,p \in \nabla} D_{ap} \log(\lambda_{ap}) - \lambda_{ap} Y_{ap} + \sum_{a,p \in \triangle} D_{ap} \log(\lambda_{ap}) - \lambda_{ap} Y_{ap}$$

No common parameters between terms  
 — we have two separate models:  
 One for upper triangles, one for lower.

### APC-model with “synthetic” cohorts

```
> mc <- glm( D ~ factor(A5) - 1 +
+           factor(P5-A5) +
+           factor(P5) + offset( log( Y ) ),
+           family=poisson )
> summary( mc )
...
Null deviance: 1.0037e+08 on 220 degrees of freedom
Residual deviance: 8.8866e+02 on 182 degrees of freedom
```

No. parameters: 220 – 182 = 38.

$$A = 10, \quad P = 11, \quad C = 20 \Rightarrow A + P + C - 3 = 38$$

### Illustration by lung cancer data

```
> library( Epi )
> data( lungDK )
> lungDK[1:10,]
  A5  P5  C5 up   Ax      Px      Cx  D      Y
1  40 1943 1898 1 43.33333 1944.667 1901.333 52 336233.8
2  40 1943 1903 0 41.66667 1946.333 1904.667 28 357812.7
3  40 1948 1903 1 43.33333 1949.667 1906.333 51 363783.7
4  40 1948 1908 0 41.66667 1951.333 1909.667 30 390985.8
5  40 1953 1908 1 43.33333 1954.667 1911.333 50 391925.3
6  40 1953 1913 0 41.66667 1956.333 1914.667 23 377515.3
7  40 1958 1913 1 43.33333 1959.667 1916.333 56 365575.5
8  40 1958 1918 0 41.66667 1961.333 1919.667 43 383689.0
9  40 1963 1918 1 43.33333 1964.667 1921.333 44 385878.5
10 40 1963 1923 0 41.66667 1966.333 1924.667 38 371361.5
```

### APC-model with “correct” cohorts

```
> mx <- glm( D ~ factor(Ax) - 1 +
+           factor(Cx) +
+           factor(Px) + offset( log( Y ) ),
+           family=poisson )
> summary( mx )
...
Null deviance: 1.0037e+08 on 220 degrees of freedom
Residual deviance: 2.8473e+02 on 144 degrees of freedom
```

No. parameters: 220 – 144 = 76 (= 38 × 2).

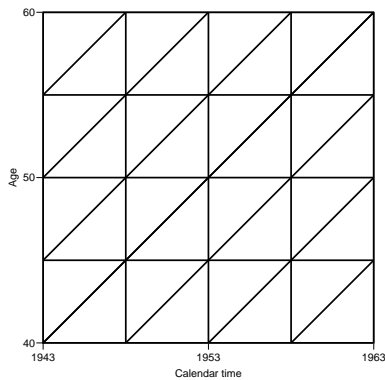
$$A = 20, \quad P = 22, \quad C = 40 \Rightarrow A + P + C - 3 = 79 \neq 76!$$

We have fitted two age-period-cohort models separately to upper and lower triangles.

Fill in the number of cases (D) and person-years (Y) from previous slide.

Indicate birth cohorts on the axes for upper and lower triangles.

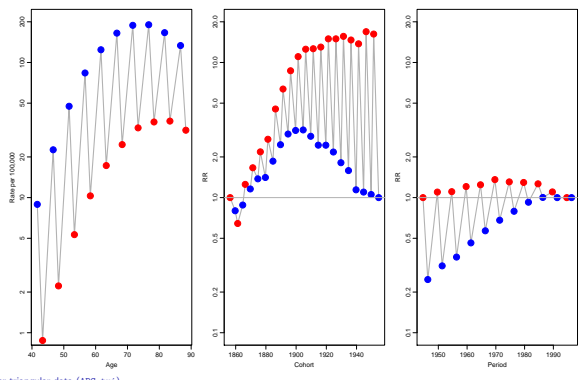
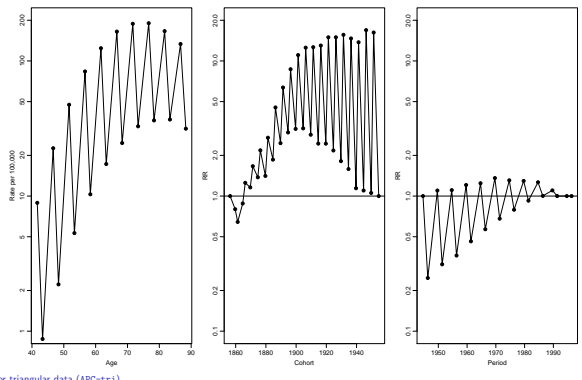
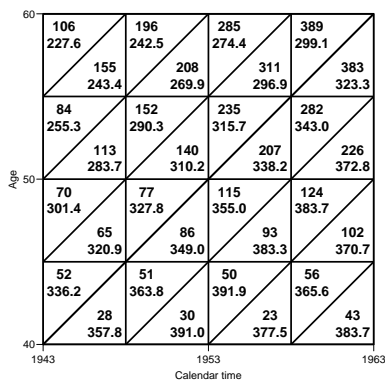
Mark mean date of birth for these.



Fill in the number of cases (D) and person-years (Y) from previous slide.

Indicate birth cohorts on the axes for upper and lower triangles.

Mark mean date of birth for these.



Now, explicitly fit models for upper and lower triangles:

```
> mx.u <- glm( D ~ factor(Ax) - 1 +
+             factor(Cx) +
+             factor(Px) + offset( log( Y/10^5 ) ), family=poisson,
+             data=lungDK[lungDK$sup==1,] )
> mx.l <- glm( D ~ factor(Ax) - 1 +
+             factor(Cx) +
+             factor(Px) + offset( log( Y/10^5 ) ), family=poisson,
+             data=lungDK[lungDK$sup==0,] )
> mx$deviance
[1] 284.7269
> mx.l$deviance
[1] 134.4566
> mx.u$deviance
[1] 150.2703
> mx.l$deviance+mx.u$deviance
[1] 284.7269
```

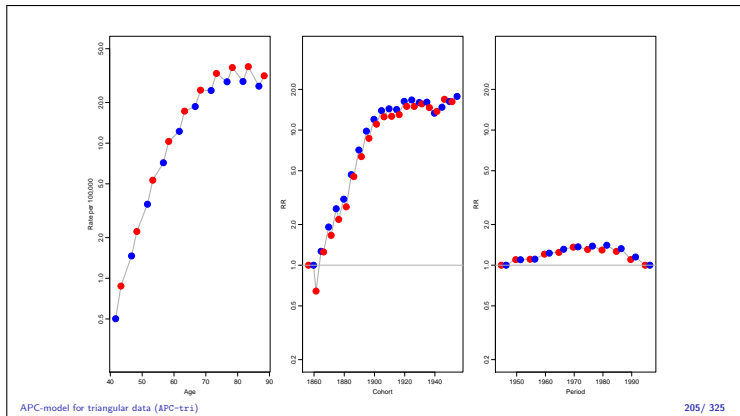
## Testis cancer

Testis cancer in Denmark:

```
> library( Epi )
> data( testisDK )
> str( testisDK )

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

> head( testisDK )
  A P D Y
1 0 1943 1 39649.50
2 1 1943 1 36942.83
3 2 1943 0 34588.33
4 3 1943 1 33267.00
5 4 1943 0 32614.00
6 5 1943 0 32020.33
```



## Cases, PY and rates

```
> print(
+ stat.table( list( A = floor(A/10)*10,
+                 P = floor(P/10)*10,
+                 list( D = sum(D),
+                       Y = sum(Y/1000),
+                       rate = ratio(D,Y,10^6) ),
+                 margins = TRUE, data = testisDK ), digits=c(sum=0,ratio=2) )
```

A	P						Total
	1940	1950	1960	1970	1980	1990	
0	10	7	16	18	9	10	70
	2605	4037	3885	3821	3071	2166	19584
	3.84	1.73	4.12	4.71	2.93	4.62	3.57
10	13	27	37	72	97	75	321
	2136	3505	4004	3906	3847	2261	19659
	6.09	7.70	9.24	18.43	25.21	33.17	16.33
20	124	221	280	535	724	557	2441
	2006	2892	3490	4090	3044	2895	19245

## Modeling for Lexis triangles

- ▶ Modeling by factors not possible
- ▶ Two separate models that cannot be fitted together
- ▶ We are not using the **quantitative** values of age, period and cohort.
- ▶ **Solution:** parametric models using the quantitative nature of  $a$ ,  $p$  and  $c = p - a$ .
- ▶ ... so we need to handle smooth parametric functions.

## Linear effects in glm

How do rates depend on age?

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

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

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

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

Linear increase of log-rates by age

## Non-linear effects

### Bendix Carstensen

Statistical Analysis in the Lexis Diagram:

Age-Period-Cohort models

— and some cousins

European Doctoral School of Demography, Odense,

June 2018

<http://BendixCarstensen/APC/EDSD-2018>

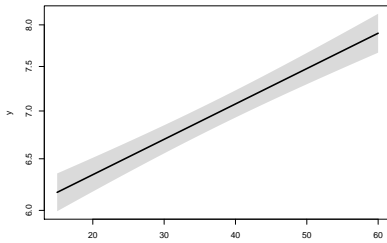
## Linear effects in glm

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

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

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

## Linear effects in glm

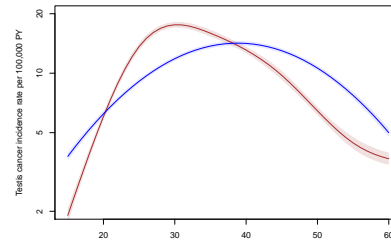


```
> nd <- data.frame( A=15:60, Y=10^-5 )
> pr <- ci.pred( ml, newdata=nd )
> matshade( nd$A, pr, plot=TRUE, lwd=3, log="y" )
```

Non-linear effects (crr-mod)

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## Spline effects in glm



```
> matshade( nd$A, cbind( ci.pred(ms,nd), ci.pred(mq,nd)), plot=TRUE,
+ log="y", xlab="Age", ylab="Testis cancer incidence rate per 100,000 PY",
+ col=c("brown","blue"), alpha=c(15,10)/100, ylim=c(2,20) )
```

Non-linear effects (crr-mod)

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## Quadratic effects in glm

How do rates depend on age?

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

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

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

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

Non-linear effects (crr-mod)

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## Adding a linear period effect

```
> msp <- glm( D ~ Ns(A,knots=seq(15,65,10)) + P,
+ offset=log(Y), family=poisson, data=testisDK )
> nd <- data.frame( A=15:60, Y=10^-5, P=1970 )
```

A multiplicative model:

$$\lambda(a, p) = f(a) \times g(p), \quad g(p_{ref}) = 1$$

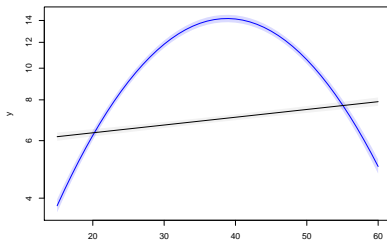
$f(a)$ : Rate at  $p_{ref}$

$g(p)$ : Rate ratio relative to  $p_{ref}$

Non-linear effects (crr-mod)

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## Quadratic effect in glm

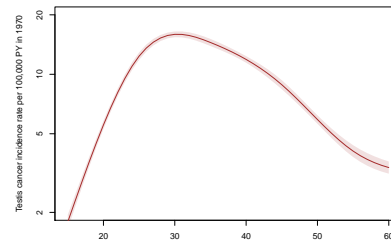


```
> matshade( nd$A, cbind( ci.pred(mq,nd), ci.pred(ml,nd) ), plot=TRUE,
+ log="y", col=c("blue","black"), alpha=c(15,5)/100 )
```

Non-linear effects (crr-mod)

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## Adding a linear period effect



```
> matshade( nd$A, ci.pred(msp,nd), plot=TRUE,
+ log="y", xlab="Age", ylim=c(2,20), col="brown", alpha=0.15,
+ ylab="Testis cancer incidence rate per 100,000 PY in 1970" )
```

Non-linear effects (crr-mod)

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## Spline effects in glm

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

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

> matplot( nd$A, ci.pred( ms, nd ),
+ log="y", xlab="Age", ylab="Testis cancer incidence rate per 100,000 PY",
+ type="l", lty=1, lwd=c(3,1,1), col="black", ylim=c(2,20) )
```

Non-linear effects (crr-mod)

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## The period effect

```
> nd.p <- data.frame( P=1945:1995 )
> nd.r <- data.frame( P=1970 )
> str( nd.p )

'data.frame': 51 obs. of 1 variable:
 $ P: int 1945 1946 1947 1948 1949 1950 1951 1952 1953 1954 ...

> str( nd.r )

'data.frame': 1 obs. of 1 variable:
 $ P: num 1970

> RR <- ci.exp( msp, ctr.mat=list(nd.p,nd.r), xvars="A" )
> matshade( nd.p$P, RR, plot=TRUE,
+ log="y", xlab="Date", ylab="Testis cancer incidence RR",
+ type="l", lty=1, lwd=c(3,1,1), col="black" )
> abline( v=1970, h=1, col="red" )
```

Non-linear effects (crr-mod)

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## A quadratic period effect

```
> mspq <- glm( D ~ Ns(A,knots=seq(15,65,10)) + P + I(P^2),
+             offset=log(Y), family=poisson, data=testisDK )
> round( ci.exp( mspq ), 4 )
```

	exp(Est.)	2.5%	97.5%
(Intercept)	0.0000	0.0000	0.0000
Ns(A, knots = seq(15, 65, 10))1	8.3560	7.4783	9.3366
Ns(A, knots = seq(15, 65, 10))2	5.5133	4.8290	6.2945
Ns(A, knots = seq(15, 65, 10))3	1.0060	0.8935	1.1326
Ns(A, knots = seq(15, 65, 10))4	13.4388	11.1008	16.2691
Ns(A, knots = seq(15, 65, 10))5	0.4582	0.4223	0.4971
P	2.1893	1.4566	3.2906
I(P^2)	0.9998	0.9997	0.9999

Non-linear effects (crr-mod)

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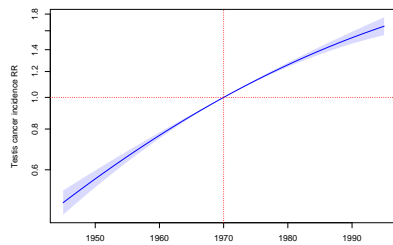
## Period effect

```
> par( mfrow=c(1,2) )
> matshade( nd$A, ci.pred( mspq, nd ), plot=TRUE,
+           log="y", xlab="Age", col="black",
+           ylab="Testis cancer incidence rate per 100,000 PY in 1970" )
> matshade( nd.p$P, ci.exp( mspq, ctr.mat=list(nd.p,nd.r), xvars="A" ), plot=TRUE
+           log="y", xlab="Date", ylab="Testis cancer incidence RR",
+           col="black" )
> abline( h=1, v=1970 )
```

Non-linear effects (crr-mod)

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## A quadratic period effect

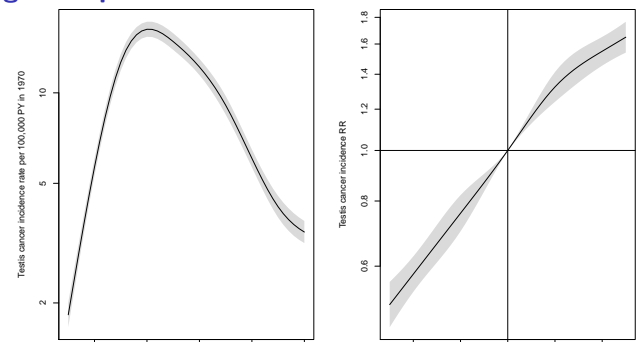


```
> matshade( nd.p$P, ci.exp( mspq, ctr.mat=list(nd.p,nd.r), xvars="A" ), plot=TRUE
+           log="y", xlab="Date", ylab="Testis cancer incidence RR", col="blue" )
> abline( h=1, v=1970, col="red", lty="13" )
```

Non-linear effects (crr-mod)

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## Age and period effect



Non-linear effects (crr-mod)

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## A spline period effect

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

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

Non-linear effects (crr-mod)

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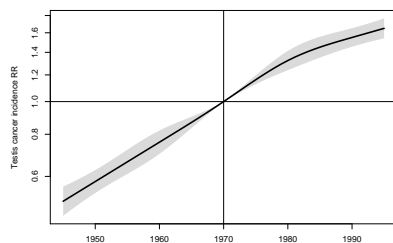
## Age and period effect with ci.exp

- ▶ In rate models there is always one term with the **rate** dimension. Usually **age**
- ▶ But it must refer to specific **reference** values for **all other** variables (in this case only P).
- ▶ For the "other" variables, report the RR **relative** to the reference point.
- ▶ Only parameters relevant for the variable (P) actually used in the calculation.
- ▶ We are essentially computing the difference between two predictions.

Non-linear effects (crr-mod)

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## Period effect



```
> matshade( nd.p$P, ci.exp( mspq, ctr.mat=list(nd.p,nd.r), xvars="A" ), plot=TRUE
+           log="y", xlab="Date", ylab="Testis cancer incidence RR", lwd=3 )
> abline( h=1, v=1970 )
```

Non-linear effects (crr-mod)

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## APC-model: Parametrization

### Bendix Carstensen

Statistical Analysis in the  
Lexis Diagram:

Age-Period-Cohort models

— and some cousins

European Doctoral School of Demography, Odense,  
June 2018

<http://BendixCarstensen/APC/EDSD-2018>

APC-par

## What's the problem?

- ▶ One parameter is assigned to each distinct value of the timescales, the **scale** of the variables is not used.
- ▶ The solution is to “tie together” the points on the scales together with smooth functions of the **mean** age, period and cohort with three functions:

$$\lambda_{ap} = f(a) + g(p) + h(c)$$

- ▶ The practical problem is how to choose a reasonable parametrization of these functions, and how to get estimates.

## Parametrization principle

1. The age-function should be interpretable as log age-specific rates in a cohort  $c_0$  after adjustment for the period effect.
2. The cohort function is 0 at a reference cohort  $c_0$ , interpretable as log-RR relative to cohort  $c_0$ .
3. The period function is 0 on average with 0 slope, interpretable as log-RR relative to the age-cohort prediction. (residual log-RR).

This will yield cohort age-effects a.k.a. **longitudinal** age effects.

Biologically interpretable:

— what happens during the lifespan of a cohort?

## The identifiability problem still exists:

$$c = p - a \Leftrightarrow p - a - c = 0$$

$$\begin{aligned} \lambda_{ap} &= f(a) + g(p) + h(c) \\ &= f(a) + g(p) + h(c) + \gamma(p - a - c) \\ &= f(a) - \mu_a - \gamma a + \\ &\quad g(p) + \mu_a + \mu_c + \gamma p + \\ &\quad h(c) - \mu_c - \gamma c \end{aligned}$$

A decision on parametrization is needed.  
... it must be **external to the model**.

## Period-major parametrization

- ▶ Alternatively, the period function could be constrained to be 0 at a reference date,  $p_0$ .
- ▶ Then, age-effects at  $a_0 = p_0 - c_0$  would equal the fitted rate for period  $p_0$  (and cohort  $c_0$ ), and the period effects would be residual log-RRs relative to  $p_0$ .
- ▶ Gives period or **cross-sectional** age-effects
- ▶ Bureaucratically interpretable:  
— what was seen at a particular date?

## Smooth functions

$$\log(\lambda(a, p)) = f(a) + g(p) + h(c)$$

Possible choices for non-linear parametric functions describing the effect of the three **quantitative** variables:

- ▶ Polynomials / fractional polynomials.
- ▶ Linear / quadratic / cubic splines.
- ▶ Natural splines.

All of these contain the linear effect as special case.

## Implementation:

1. Obtain any set of parameters  $f(a)$ ,  $g(p)$ ,  $h(c)$ .
2. Extract the trend from the period effect (find  $\mu$  and  $\beta$ ):

$$\tilde{g}(p) = \hat{g}(p) - (\mu + \beta p)$$

3. Decide on a reference cohort  $c_0$ .
4. Use the functions:

$$\begin{aligned} \tilde{f}(a) &= \hat{f}(a) + \mu + \beta a + \hat{h}(c_0) + \beta c_0 \\ \tilde{g}(p) &= \hat{g}(p) - \mu - \beta p \\ \tilde{h}(c) &= \hat{h}(c) + \beta c - \hat{h}(c_0) - \beta c_0 \end{aligned}$$

## Parametrization of effects

There are still three “free” parameters:

$$\begin{aligned} \tilde{f}(a) &= f(a) - \mu_a - \gamma a \\ \tilde{g}(p) &= g(p) + \mu_a + \mu_c + \gamma p \\ \tilde{h}(c) &= h(c) - \mu_c - \gamma c \end{aligned}$$

**Any** set of 3 numbers,  $\mu_a$ ,  $\mu_c$  and  $\gamma$  will produce effects with the same sum:

$$\tilde{f}(a) + \tilde{g}(p) + \tilde{h}(c) = f(a) + g(p) + h(c)$$

The problem is to choose  $\mu_a$ ,  $\mu_c$  and  $\gamma$  according to some criterion for the functions.

## “Extract the trend”

- ▶ **Not** a well-defined concept:
  - ▶ Regress  $\hat{g}(p)$  on  $p$  for all units in the dataset.
  - ▶ Regress  $\hat{g}(p)$  on  $p$  for all different values of  $p$ .
  - ▶ Weighted regression — what weights?
- ▶ How do we get the standard errors?
- ▶ Matrix-algebra!
- ▶ Projections!
- ▶ Weighted inner product...

## Parametric function

Suppose that  $g(p)$  is parametrized using the design matrix  $\mathbf{M}$ , with the estimated parameters  $\pi$ .

Example: 2nd degree polynomial:

$$\mathbf{M} = \begin{bmatrix} 1 & p_1 & p_1^2 \\ 1 & p_2 & p_2^2 \\ \vdots & \vdots & \vdots \\ 1 & p_n & p_n^2 \end{bmatrix} \quad \pi = \begin{bmatrix} \pi_0 \\ \pi_1 \\ \pi_2 \end{bmatrix} \quad g(p) = \mathbf{M}\pi$$

$\text{nrow}(\mathbf{M})$  is the no. of observations in the dataset,

$\text{ncol}(\mathbf{M})$  is the no. of parameters

## Information in the data and inner product

Log-lik for an observation  $(D, Y)$ , with log-rate  $\theta = \log(\lambda)$ :

$$l(\theta|D, Y) = D\theta - e^\theta Y, \quad l'_\theta = D - e^\theta Y, \quad l''_\theta = -e^\theta Y$$

so  $I(\hat{\theta}) = e^{\hat{\theta}} Y = \hat{\lambda} Y = D$ .

Log-lik for an observation  $(D, Y)$ , with rate  $\lambda$ :

$$l(\lambda|D, Y) = D\log(\lambda) - \lambda Y, \quad l'_\lambda = D/\lambda - Y, \quad l''_\lambda = -D/\lambda^2,$$

so  $I(\hat{\lambda}) = D/\hat{\lambda}^2 = Y^2/D (= Y/\hat{\lambda})$

## Extract the trend from $g$ :

Vectors  $\mathbf{x}$  and  $\mathbf{y}$  are orthogonal if the inner product is 0

$$\mathbf{x} \perp \mathbf{y} \Leftrightarrow \langle \mathbf{x} | \mathbf{y} \rangle = \sum_i x_i y_i = 0$$

- ▶  $\langle \tilde{g}(p) | 1 \rangle = 0, \langle \tilde{g}(p) | p \rangle = 0$ , i.e.  $\tilde{g}$  is **orthogonal** to  $[1:p]$ .
- ▶ Suppose  $\tilde{g}(p) = \tilde{\mathbf{M}}\pi$ , then for **any** parameter vector  $\pi$ :  
 $\langle \tilde{\mathbf{M}}\pi | 1 \rangle = 0, \langle \tilde{\mathbf{M}}\pi | p \rangle = 0 \implies \tilde{\mathbf{M}} \perp [1:p]$
- ▶ Thus we just need to be able to produce  $\tilde{\mathbf{M}}$  from  $\mathbf{M}$ :  
 Projection on the orthogonal complement of  $\text{span}([1:p])$ .
- ▶ **But:** orthogonality requires an inner product!

## Information in the data and inner product

▶ Inner products:

$$\langle \mathbf{m}_j | \mathbf{m}_k \rangle = \sum_i m_{ij} m_{ik} \quad \langle \mathbf{m}_j | \mathbf{m}_k \rangle = \sum_i m_{ij} w_i m_{ik}$$

▶ Weights could be chosen as:

- ▶  $w_i = D_i$ , i.e. proportional to the information content for  $\theta = \log(\lambda)$ ,  
`dr.extr` in  $\{\mathbf{w}, \mathbf{t}, \mathbf{d}\}$  (the default)
- ▶  $w_i = Y_i^2/D_i$ , i.e. proportional to the information content for  $\lambda$ ,  
`dr.extr` in  $\{\mathbf{1}, \mathbf{r}\}$
- ▶  $w_i = Y_i$ , i.e. proportional to the persons years, approximation  
 proportionality to the no. persons contributing,  $\{\mathbf{dr.extr} \in \{\mathbf{y}\}\}$
- ▶  $w_i = 1$ , the "usual" inner product — implicitly used in most of the  
 literature — any other value for `dr.extr`.

## Practical parametrization

1. Set up model matrices for age, period and cohort,  $M_a, M_p$  and  $M_c$ . Intercept in all three.
2. Extract the linear trend from  $M_p$  and  $M_c$ , by projecting their columns onto the orthogonal complement of  $[1:p]$  and  $[1:c]$ , respectively
3. Center the cohort effect around  $c_0$ :  
 Take a row from  $\tilde{M}_c$  corresponding to  $c_0$ , replicate to dimension as  $\tilde{M}_c$ , and subtract it from  $\tilde{M}_c$  to form  $\tilde{M}_{c_0}$ .

## How to? I

Implemented in `apc.fit` in the Epi package:

```
> library( Epi )
> library( splines )
> data( lungDK )
> mw <- apc.fit( A = lungDK$Ax,
+               P = lungDK$Px,
+               D = lungDK$D,
+               Y = lungDK$Y/10^5,
+               ref.c = 1900,
+               npar = 8,
+               parm = "ACP",
+               dr.extr = "w" ) # drift extraction - choice of inner product
```

4. Use:  
 $\tilde{M}_a$  for the age-effects,  
 $\tilde{M}_p$  for the period effects and  
 $[c - c_0; \tilde{M}_{c_0}]$  for the cohort effects.
5. Value of  $\hat{f}(a)$  is  $M_a \hat{\beta}_a$ , similarly for the other two effects.  
 Variance is found by  $M'_a \hat{\Sigma}_a M_a$ , where  $\hat{\Sigma}_a$  is the  
 variance-covariance matrix of  $\hat{\beta}_a$ .

## How to? II

```
NOTE: npar is specified as: A P C
8 8 8
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"
```

```
Analysis of deviance for Age-Period-Cohort model

Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                212    15468.6
Age-drift          211    6858.9  1   8609.7 < 2.2e-16
Age-Cohort         205   1034.7  6   5824.1 < 2.2e-16
Age-Period-Cohort 199    423.2  6    611.6 < 2.2e-16
Age-Period         205   3082.6  -6  -2659.4 < 2.2e-16
Age-drift          211    6858.9  -6  -3776.3 < 2.2e-16

> plot( mw )

cp.offset  RR.fac
1765       100
```



Consult the help page for: `apc.fit` to see options for weights in inner product, type of function, variants of parametrization etc. `apc.plot`, `apc.lines` and `apc.frame` to see how to plot the results.

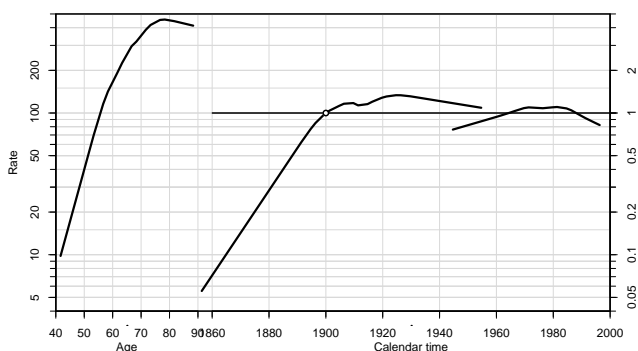
```
> my <- apc.fit( A = lungDK$Ax,
+               P = lungDK$Px,
+               D = lungDK$D,
+               Y = lungDK$Y/10^5,
+               npar = 8,
+               ref.c = 1900,
+               dr.extr = "y" ) # paerson-yeras, weight Y

NOTE: npar is specified as:A P C
8 8 8
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

      Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                212    15468.6
Age-drift          211    6858.9  1  8609.7 < 2.2e-16
Age-Cohort         205    1034.7  6  5824.1 < 2.2e-16
Age-Period-Cohort  199     423.2  6   611.6 < 2.2e-16
Age-Period         205    3082.6 -6 -2659.4 < 2.2e-16
Age-drift          211    6858.9 -6 -3776.3 < 2.2e-16

> ##
```



```
> m1 <- apc.fit( A = lungDK$Ax,
+               P = lungDK$Px,
+               D = lungDK$D,
+               Y = lungDK$Y/10^5,
+               npar = 8,
+               ref.c = 1900,
+               dr.extr = "1" ) # usual inner product

NOTE: npar is specified as:A P C
8 8 8
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

      Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                212    15468.6
Age-drift          211    6858.9  1  8609.7 < 2.2e-16
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Age-Period         205    3082.6 -6 -2659.4 < 2.2e-16
Age-drift          211    6858.9 -6 -3776.3 < 2.2e-16

> ##
```

## Other models I

```
> dr <- cbind( mw$Drift, m1$Drift, my$Drift, m1$Drift )
> rownames(dr) <- c("APC extract", "Age-Drift")
> colnames(dr)[0:3*3+1] <- c("D-wt", "Y^2/D-wt", "Y-wt", "1-wt")
> round( dr, 2 )

      D-wt 2.5% 97.5% Y^2/D-wt 2.5% 97.5% Y-wt 2.5% 97.5% 1-wt 2.5% 97.5%
APC extract 1.02 1.02 1.02 1.01 1.01 1.02 1.02 1.02 1.02 1.03 1.03 1.03
Age-Drift 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.02

> # % change per year
> round( (dr-1)*100, 1 )

      D-wt 2.5% 97.5% Y^2/D-wt 2.5% 97.5% Y-wt 2.5% 97.5% 1-wt 2.5% 97.5%
APC extract 2.0 1.9 2.0 1.5 1.4 1.6 2.0 1.9 2.1 3.3 3.2 3.4
Age-Drift 2.3 2.3 2.4 2.3 2.3 2.4 2.3 2.3 2.4 2.3 2.3 2.4
```

Substantial differences between the estimated drifts.

```
> m1 <- apc.fit( A = lungDK$Ax,
+               P = lungDK$Px,
+               D = lungDK$D,
+               Y = lungDK$Y/10^5,
+               npar = 8,
+               ref.c = 1900,
+               dr.extr = "1" ) # l(ambda), the rate itself, weight Y^2/D

NOTE: npar is specified as:A P C
8 8 8
[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

      Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age                212    15468.6
Age-drift          211    6858.9  1  8609.7 < 2.2e-16
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Age-Period-Cohort  199     423.2  6   611.6 < 2.2e-16
Age-Period         205    3082.6 -6 -2659.4 < 2.2e-16
Age-drift          211    6858.9 -6 -3776.3 < 2.2e-16

> ##
```

## Parametrization of the APC model is arbitrary

- ▶ Separation of the three effects relies on arbitrary principles, e.g.:
  - ▶ Age is the primary effect
  - ▶ Cohort the secondary, reference  $c_0$
  - ▶ Period is the residual
  - ▶ Inner product for trend extraction
- ▶ There is no magical fix that allows you to escape this, it comes from modelling  $a$ ,  $p$  and  $p - a$
- ▶ Any fix has some (hidden) assumption(s)
- ▶ ... but the **fitted values** are the same

## Lee-Carter model in continuous time

$$\log(\lambda(a, t)) = f(a) + b(a) \times k(t)$$

- ▶ Lee-Carter model is an extension of the age-period model; if  $b(a) = 1$  it **is** the age-period model.
- ▶ The extension is an age  $\times$  period interaction, but not a traditional one:
 
$$\log(\lambda(a, t)) = f(a) + b(a) \times k(t) = f(a) + k(t) + (b(a) - 1) \times k(t)$$
- ▶ Main effect and interaction component of  $t$  are constrained to be identical.

## Lee-Carter model

Bendix Carstensen

Statistical Analysis in the Lexis Diagram:

Age-Period-Cohort models  
— and some cousins

European Doctoral School of Demography, Odense,  
June 2018

<http://BendixCarstensen/APC/EDSD-2018>

LeeCarter

## Main effect and interaction term

Main effect and interaction component of  $t$  are constrained to be identical.

None of these are Lee-Carter models:

```
> glm( D ~ Ns(A, kn=a1.kn) + Ns(A, kn=a2.kn, i=T):Ns(P, kn=p.kn), ... )
> glm( D ~ Ns(A, kn=a1.kn) + Ns(A, kn=a2.kn, i=T)*Ns(P, kn=p.kn), ... )
> glm( D ~ Ns(A, kn=a1.kn) + Ns(P, kn=p.kn) + Ns(A, kn=a2.kn, i=T):Ns(P, kn=p.kn), ... )
```

## Lee-Carter model for (mortality) rates

Lee & Carter, JASA, 1992:

$$\log(\lambda_{x,t}) = a_x + b_x \times k_t$$

$x$  is age;  $t$  is calendar time

- ▶ Formulated originally using as step-functions with one parameter per age/period.
- ▶ Implicitly assumes a data lay out by age and period: A, B or C-sets, but **not** Lexis triangles
- ▶ Using Lexis triangles with categorical set-up would just produce separate models for upper and lower triangles.

## Lee-Carter model interpretation

$$\log(\lambda(a, p)) = f(a) + b(a) \times k(p)$$

- ▶ Constraints:
- ▶  $f(a)$  is the basic age-specific mortality
- ▶  $k(p)$  is the rate-ratio (RR) as a function of  $p$ :
  - ▶ relative to a  $p_{ref}$  where  $k(p_{ref}) = 1$
  - ▶ for persons aged  $a_{ref}$  where  $b(a_{ref}) = 1$
- ▶  $b(a)$  is an age-specific multiplier for the RR  $k(p)$
- ▶ Choose  $p_{ref}$  and  $a_{ref}$  a priori.

## Lee-Carter model in continuous time

For **any** set of subsets of a Lexis diagram:

$$\log(\lambda(a, t)) = f(a) + b(a) \times k(t)$$

- ▶  $f(a)$ ,  $b(a)$  smooth functions of age,  $a$  is **quantitative**
- ▶  $k(t)$  smooth function of period,  $t$  is **quantitative**
- ▶ Relative **scaling** of  $b(a)$  and  $k(t)$  cannot be determined
- ▶  $k(t)$  only determined up to an **affine** transformation:

$$\begin{aligned} f(a) + b(a)k(t) &= f(a) + (b(a)/n)(m + k(t) \times n) \\ &\quad - (b(a)/n) \times m \\ &= \tilde{f}(a) + \tilde{b}(a)\tilde{k}(t) \end{aligned}$$

## Danish lung cancer data I

```
> lung <- read.table( "../data/apc-Lung.txt", header=T )
> head( lung )
  sex A   P   C D   Y
1  1  0 1943 1942 0 19546.2
2  1  0 1943 1943 0 20796.5
3  1  0 1944 1943 0 20681.3
4  1  0 1944 1944 0 22478.5
5  1  0 1945 1944 0 22369.2
6  1  0 1945 1945 0 23885.0

> # Only A by P classification - and only men over 40
> ltab <- xtabs( cbind(D,Y) ~ A + P, data=subset(lung,sex=1) )
> str( ltab )
```

## Danish lung cancer data II

```
xtabs [1:90, 1:61, 1:2] 0 0 0 0 0 0 0 0 0 ...
- attr(*, "dimnames")=List of 3
..$ A: chr [1:90] "0" "1" "2" "3" ...
..$ P: chr [1:61] "1943" "1944" "1945" "1946" ...
..$ : chr [1:2] "D" "Y"
- attr(*, "call")= language xtabs(formula = cbind(D, Y) ~ A + P, data = subset(L
```

Lee-Carter modeling in R-packages:

- ▶ demography (`lca`)
- ▶ ilc (`lca.rh`)
- ▶ Epi (`LCa.fit`).

## Lee-Carter re-scaled I

$$\log(\hat{\lambda}(a, p)) = [f(a) + b(a) \times 20] + [b(a) \times 50] \times [(k(t) - 20)/50]$$

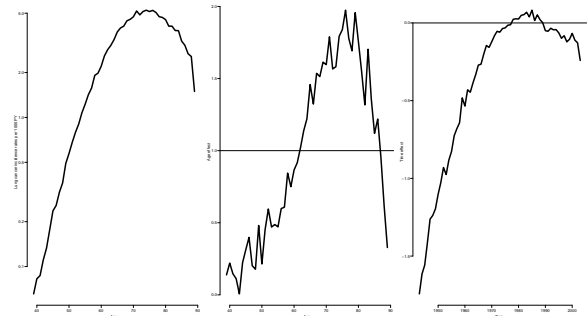
```
> par( mfc=c(1,3) )
> matplot( dmg.lcM$age, exp(dmg.lcM$ax+dmg.lcM$bx*20)*1000,
+         log="y", ylab="Lung cancer incidence rates per 1000 PY",
+         xlab="Age", type="l", lty=1, lwd=4 )
> matplot( dmg.lcM$age, dmg.lcM$bx*50,
+         ylab="Age effect",
+         xlab="Age", type="l", lty=1, lwd=4 )
> abline(h=1)
> matplot( dmg.lcM$year, (dmg.lcM$kt-20)/50,
+         ylab="Time effect",
+         xlab="Date", type="l", lty=1, lwd=4 )
> abline(h=0)
```

## Lee-Carter with demography I

```
> library(demography)
> lcM <- demogdata( data = as.matrix(ltab[40:90, "D"]/ltab[40:90, "Y"]),
+                 pop = as.matrix(ltab[40:90, "Y"]),
+                 ages = as.numeric(dimnames(ltab)[1][40:90]),
+                 years = as.numeric(dimnames(ltab)[2]),
+                 type = "Lung cancer incidence",
+                 label = "Denmark",
+                 name = "Male" )
```

`lca` estimation function checks the `type` argument, so we make a work-around, `mrt`:

## Lee-Carter with demography rescaled



## Lee-Carter with demography II

```
> mrt <- function(x) { x$type <- "mortality"; x }
> dmg.lcM <- lca( mrt(lcM), interpolate=TRUE )
> par( mfc=c(1,3) )
> matplot( dmg.lcM$age, exp(dmg.lcM$ax)*1000,
+         log="y", ylab="Lung cancer incidence rates per 1000 PY",
+         xlab="Age", type="l", lty=1, lwd=4 )
> matplot( dmg.lcM$age, dmg.lcM$bx,
+         ylab="Age effect",
+         xlab="Age", type="l", lty=1, lwd=4 )
> matplot( dmg.lcM$year, dmg.lcM$kt,
+         ylab="Time effect",
+         xlab="Date", type="l", lty=1, lwd=4 )
> abline(h=0)
```

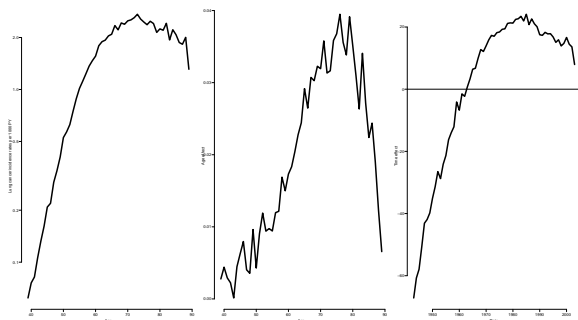
## Lee-Carter with ilc

- ▶ The `lca.rh` function fits the model using maximum likelihood (proportional scaling)
- ▶ Fits the more general model and submodels of it:

$$\log(\lambda(a, p)) = f(a) + b(a) \times k(p) + c(a)m(p - a)$$

- ▶ Age interaction with between age and both period and/or cohort (=period-age)
  - ▶ It is also an extension of the APC-model; if  $b(a) = 1$  and  $c(a) = 1$  it's the APC-model.
- ⇒ suffers from the same identifiability problem

## Lee-Carter with demography



## Lee-Carter with ilc I

```
> library( ilc )
> ilc.lcM <- lca.rh( mrt(lcM), model="lc", interpolate=TRUE, verbose=FALSE )

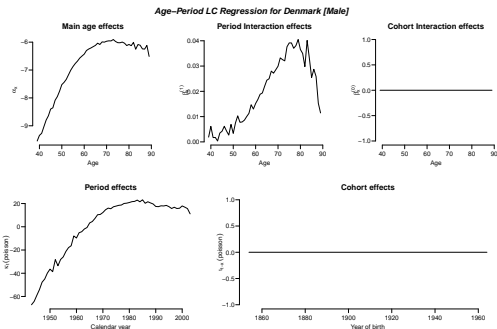
Original sample: Mortality data for Denmark
Series: Male
Years: 1943 - 2003
Ages: 39 - 89
Applied sample: Mortality data for Denmark (Corrected: interpolate)
Series: Male
Years: 1943 - 2003
Ages: 39 - 89

Fitting model: [ LC = a(x)+b1(x)*k(t) ]
- with poisson error structure and with deaths as weights -

Iterations finished in: 34 steps

> plot( ilc.lcM )
```

## Lee-Carter with ilc



Lee-Carter model (LeeCarter)

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## Lee-Carter and the APC-model

- ▶ Lee-Carter model is an interaction extension of the Age-Period model
- ▶ ... or an interaction extension of the Age-Cohort model
- ▶ Age-Period-Cohort model is:
  - ▶ interaction extension
  - ▶ the smallest **union** of Age-Period and Age-Cohort
- ▶ Extended Lee-Carter (from the `ilc` package)

$$\log(\lambda(a, p)) = f(a) + b(a) \times k(p) + c(a)m(p - a)$$

is the union of all of these.

Lee-Carter model (LeeCarter)

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## Lee-Carter with Epi

- ▶ `LCa.fit` fits the Lee-Carter model using natural splines for the **quantitative** effects of age and time.
- ▶ Normalizes effects to a reference age and period.
- ▶ The algorithm alternately fits a main age and period effects and the age-interaction effect.

$$\log(\lambda(a, p)) = f(a) + b(a) \times k(p) + c(a) \times m(p - a)$$

$$\log(\lambda(a, p)) = f(a) + b(a) \times k(p) + c(a) \times m(p - a)$$

Lee-Carter model (LeeCarter)

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## Lee-Carter and the APC-model

```
> system.time( allmod <- apc.LCa( Mlc, keep.models=TRUE ) )
> str( allmod )
> save( allmod, file='allmod.Rda' )

> load( file='allmod.Rda' )
> show.apc.LCa( allmod, top="Ad" )

> show.apc.LCa( allmod, top="AP" )

> show.apc.LCa( allmod, top="AC" )
```

Lee-Carter model (LeeCarter)

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## Lee-Carter with Epi I

```
> library( Epi )
> Mlc <- subset( lung, sex==1 & A>39 )
> LCa.Mlc <- LCa.fit( Mlc, a.ref=60, p.ref=1980 )

LCa.fit convergence in 8 iterations, deviance: 8548.443 on 6084 d.f.

> LCa.Mlc

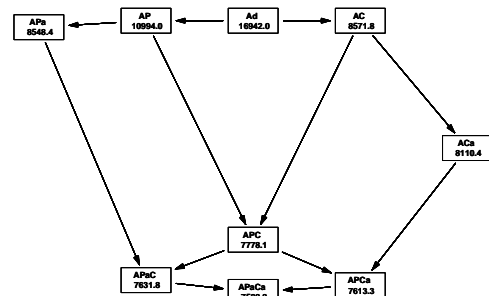
APa: Lee-Carter model with natural splines:
log(Rate) = ax(Age) + pi(Age)kp(Per)
with 6, 5 and 5 parameters respectively.
Deviance: 8548.443 on 6084 d.f.

> plot( LCa.Mlc, rnam="Lung cancer incidence per 1000 PY" )
```

Lee-Carter model (LeeCarter)

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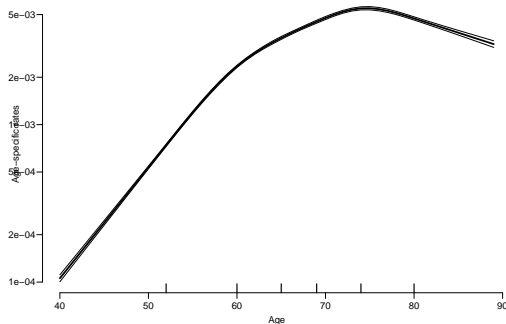
## Lee-Carter models and APC models



Lee-Carter model (LeeCarter)

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## Lee-Carter with Epi



Lee-Carter model (LeeCarter)

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## Lee-Carter models and APC models

- ▶ The classical Lee-Carter model is an extension of the Age-Period model with an interaction
- ▶ The Age-Period-Cohort model is an extension of the Age-Period model with an interaction
- ▶ Replacing period with cohort gives another type of Lee-Carter model
- ▶ The logical step is to consider all 9 models that comes from cross-classification of how the interaction term  $b(a)$ 
  - ▶ Linear effect ( $b(a) = 0$ )
  - ▶ Non-linear effect ( $b(a) = 1$ )
  - ▶ Multiplicative interaction with age ( $b(a)$  unconstrained)

Lee-Carter model (LeeCarter)

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## Lee-Carter models and APC models

		$b_c(a)$		
		0	1	free
	0	Age	Age+Coh	LCa(C) <i>AC, ac, ACa</i>
$b_p(a)$	1	Age+Per	Age+Per+Coh $H_0, h_0$	Age+Per+LCa(C) $H_1, h_1, APCa$
	free	LCa(P) <i>LC, lc, APa</i>	Age+Coh+LCa(P) $H_2, h_2, APaC$	Age+LCa(P)+LCa(C) <i>M, m, APaCa</i>

Model: `ilc: lca.rh( model= )` `Epi: LCa.fit( model= )`

## Two sets of data II

```
> head( th )
  a  p  c  y  age  diag  birth hist d
1 0 1943 1942 18853.0 0.6666667 1943.333 1942.667 1 0
2 0 1943 1942 18853.0 0.6666667 1943.333 1942.667 2 1
3 0 1943 1942 18853.0 0.6666667 1943.333 1942.667 3 0
4 0 1943 1943 20796.5 0.3333333 1943.667 1943.333 1 0
5 0 1943 1943 20796.5 0.3333333 1943.667 1943.333 2 0
6 0 1943 1943 20796.5 0.3333333 1943.667 1943.333 3 0

> th <- transform( th,
+                 hist = factor( hist, labels=c("Sem", "nS", "Oth" ) ),
+                 A = age,
+                 P = diag,
+                 D = d,
+                 Y = y/10^4 ), c("A", "P", "D", "Y", "hist"))
> th <- subset( th, A>15 & A<65 & hist!="Oth" )
> th$hist <- factor( th$hist )
```

## APC-models for several datasets

### Bendix Carstensen

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Lexis Diagram:

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<http://BendixCarstensen/APC/EDSD-2018>

```
> library( Epi )
> stat.table( list( Histology = hist ),
+            list( D = sum(D),
+                 Y = sum(Y) ),
+            margins = TRUE,
+            data = th )
```

Histology	D	Y
Sem	4461.00	8435.49
nS	3494.00	8435.49
Total	7955.00	16870.99

First step is separate analyses for each subtype (Sem, nS, resp.)

## Two APC-models

- ▶ APC-models for two sets of rates (men/women, say)

$$\log(\lambda_i(a, p)) = f_i(a) + g_i(p) + h_i(p - a), \quad i = 1, 2$$

- ▶ Rate-ratio also an APC-model:

$$\begin{aligned} \log(\text{RR}(a, p)) &= \log(\lambda_1(a, p)) - \log(\lambda_2(a, p)) \\ &= (f_1(a) - f_2(a)) + (g_1(p) - g_2(p)) \\ &\quad + (h_1(p - a) - h_2(p - a)) \\ &= f_{\text{RR}}(a) + g_{\text{RR}}(p) + h_{\text{RR}}(p - a) \end{aligned}$$

- ▶ Model the two sets of rates separately and report the ratio effects as any other APC-model.
- ▶ Note; not all constraints carry over to RR

```
> apc.Sem <- apc.fit( subset( th, hist=="Sem" ),
+                   parm = "ACP",
+                   ref.c = 1970,
+                   npar = c(A=8, P=8, C=8) )

[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

Age          Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age-drift    5392      5677.5
Age-Cohort   5391      5074.1  1   603.33 < 2.2e-16
Age-Period   5385      5038.7  6   35.47 3.495e-06
Age-Period-Cohort 5379      5014.7  6   24.01 0.0005201
Age-Period   5385      5061.5 -6   -46.80 2.049e-08
Age-drift    5391      5074.1 -6   -12.68 0.0484745
```

## Two sets of data I

Example: Testis cancer in Denmark, Seminoma and non-Seminoma cases.

```
> th <- read.table( "../data/testis-hist.txt", header=TRUE )
> str( th )

'data.frame': 29160 obs. of 9 variables:
 $ a : int 0 0 0 0 0 1 1 1 1 ...
 $ p : int 1943 1943 1943 1943 1943 1943 1943 1943 1943 ...
 $ c : int 1942 1942 1942 1943 1943 1943 1941 1941 1941 1942 ...
 $ y : num 18853 18853 18853 20796 20796 ...
 $ age : num 0.667 0.667 0.667 0.333 0.333 ...
 $ diag : num 1943 1943 1943 1944 1944 ...
 $ birth: num 1943 1943 1943 1943 1943 ...
 $ hist : int 1 2 3 1 2 3 1 2 3 1 ...
 $ d : int 0 1 0 0 0 0 0 0 0 ...
```

```
> apc.nS <- apc.fit( subset( th, hist=="nS" ),
+                   parm = "ACP",
+                   ref.c = 1970,
+                   npar = c(A=8, P=8, C=8) )

[1] "ML of APC-model Poisson with log(Y) offset : ( ACP ):\n"

Analysis of deviance for Age-Period-Cohort model

Age          Resid. Df Resid. Dev Df Deviance Pr(>Chi)
Age-drift    5392      5202.5
Age-Period   5391      4501.5  1   701.08 < 2.2e-16
Age-Cohort   5385      4459.7  6   41.77 2.046e-07
Age-Period-Cohort 5379      4375.2  6   84.53 4.133e-16
Age-Period   5385      4427.6 -6   -52.43 1.531e-09
Age-drift    5391      4501.5 -6   -73.87 6.563e-14

> round( (cbind( apc.Sem$Drift,
+               apc.nS$Drift ) - 1)*100, 1 )
```

```

exp(Est.) 2.5% 97.5% exp(Est.) 2.5% 97.5%
APC (D-weights) 2.5 2.3 2.7 3.1 2.8 3.3
A-d 2.5 2.3 2.7 3.1 2.8 3.3

```

```

> plot( apc.Sem, "Sem vs. non-Sem RR", col="transparent" )

cp.offset  RR.fac
1804      1

> matshade( apc.n$Age[1], ci.ratio( apc.Sem$Age[-1], apc.n$Age[-1] ), col=1 )
> pc.matshade( apc.n$Per[1], ci.ratio( apc.Sem$Per[-1], apc.n$Per[-1] ), col=1 )
> pc.matshade( apc.n$Coh[1], ci.ratio( apc.Sem$Coh[-1], apc.n$Coh[-1] ), col=1 )
> abline( h=1 )

```

## Analysis of two rates: Formal tests II

```

> apc.ns <- apc.fit( subset(th,hist=="nS" ), npar=list(A=Akn,P=Pkn,C=Ckn), pr=F )

```

No reference period given:  
Reference period for age-effects is chosen as  
the median date of birth for persons with event: 1949.667 .

Joint model, parametrize interactions separately:

## Analysis of two rates: Formal tests III

```

> Ma <- with( th, Ns( A, knots=Akn, intercept=TRUE ) )
> Mp <- with( th, Ns( P, knots=Pkn ) )
> Mc <- with( th, Ns( P-A, knots=Ckn ) )
> # extract the linear trend
> Mp <- detrend( Mp, th$P, weight=th$D )
> Mc <- detrend( Mc, th$P-th$A, weight=th$D )
> m.apc <- glm( D ~ -1 + Ma:hist + Mp:hist + Mc:hist +
+ P:hist + # note separate slopes extracted
+ offset( log(Y) ),
+ family=poisson, data=th )
> m.apc$deviance

[1] 9410.446

> # Same as the sum from separate models
> apc.ns$Model$deviance + apc.sem$Model$deviance

[1] 9410.446

```

## Analysis of two rates: Formal tests IV

Tests for equality of non-linear part of shapes

```

> m.ap <- update( m.apc, . ~ . - Mc:hist + Mc )
> m.ac <- update( m.apc, . ~ . - Mp:hist + Mp )
> m.a <- update( m.ap, . ~ . - Mp:hist + Mp )
> m.d <- update( m.ap, . ~ . - Mp:hist )
> m.o <- update( m.ap, . ~ . - P:hist + P )
> AOV <- anova( m.a, m.ac, m.apc, m.ap, m.a, m.d, m.o, test="Chisq")
> rownames( AOV ) <- c( "", "cohRR", "perRR|coh", "cohRR|per", "perRR", "drift", "Smdrift" )
> AOV

```

## Analysis of two rates: Formal tests I

Separate models with the same parametrization:

```

> ( Akn <- ( apc.Sem$Knots$Age+apc.n$Knots$Age ) / 2 )
[1] 22.66667 26.50000 29.50000 32.33333 35.16667 38.83333 43.83333 52.66667

> ( Pkn <- ( apc.Sem$Knots$Per+apc.n$Knots$Per ) / 2 )
[1] 1952.417 1964.000 1972.333 1978.167 1983.000 1987.500 1991.500 1995.000

> ( Ckn <- ( apc.Sem$Knots$Coh+apc.n$Knots$Coh ) / 2 )
[1] 1913.500 1926.000 1934.833 1942.000 1947.833 1953.333 1958.958 1966.000

> apc.sem <- apc.fit( subset(th,hist=="Sem"), npar=list(A=Akn,P=Pkn,C=Ckn), pr=F )

```

No reference period given:  
Reference period for age-effects is chosen as  
the median date of birth for persons with event: 1939.667 .

## Analysis of two rates: Formal tests V

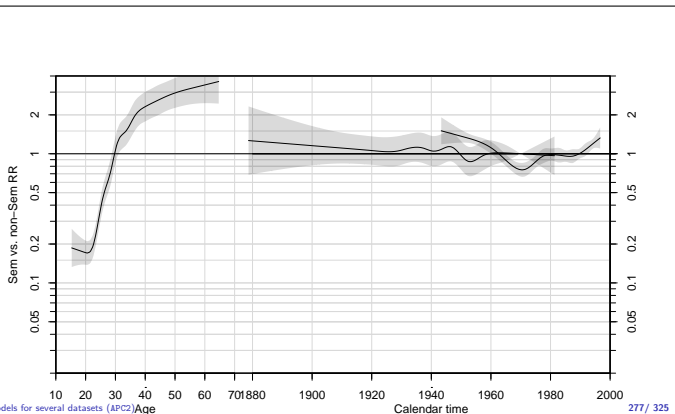
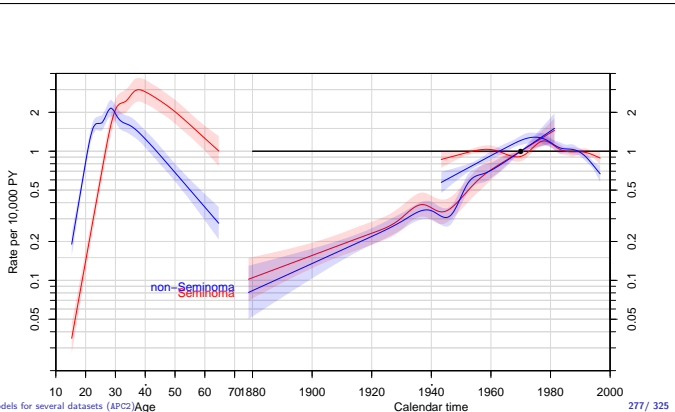
Analysis of Deviance Table

```

Model 1: D ~ Mc + Mp + Ma:hist + hist:P + offset(log(Y)) - 1
Model 2: D ~ Mp + Ma:hist + hist:Mc + hist:P + offset(log(Y)) - 1
Model 3: D ~ -1 + Ma:hist + Mp:hist + Mc:hist + P:hist + offset(log(Y)) - 1
Model 4: D ~ Mc + Ma:hist + hist:Mp + hist:P + offset(log(Y)) - 1
Model 5: D ~ Mc + Mp + Ma:hist + hist:P + offset(log(Y)) - 1
Model 6: D ~ Mc + Ma:hist + hist:P + offset(log(Y)) - 1
Model 7: D ~ Mc + P + Ma:hist + hist:Mp + offset(log(Y)) - 1

```

	Resid. Df	Resid. Dev	Df	Deviance	Pr(>Chi)
	10770	9467.4			
cohRR	10764	9447.3	6	20.094	0.002665
perRR coh	10758	9410.4	6	36.886	1.854e-06
cohRR per	10764	9421.6	-6	-11.196	0.082496
perRR	10770	9467.4	-6	-45.783	3.270e-08
drift	10776	9538.2	-6	-70.807	2.793e-13
Smdrift	10765	9425.6	11	112.612	< 2.2e-16



## Several datasets I

- ▶ Separate models for each
- ▶ Rate-ratios between two sets of fitted rates also follow an APC model
- ▶ Constraints does not necessarily carry over to RRs
- ▶ Test for equality of effects: non-linear and linear
- ▶ Take care not to violate the **principle of marginality**: — do not test linear terms when non-linear terms are in the model.

APC-models for several datasets (APC2)

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## Analysis of DM-rates: Age×sex interaction III

```
> dm <- dm[dm$cen=="D1: Denmark",]
> attach( dm )
> # Define knots and points of prediction
> n.A <- 5
> n.C <- 8
> n.P <- 5
> c0 <- 1985
> attach( dm, warn.conflicts=FALSE )
> A.kn <- quantile( rep( A, D ), probs=(1:n.A-0.5)/n.A )
> P.kn <- quantile( rep( P, D ), probs=(1:n.P-0.5)/n.P )
> C.kn <- quantile( rep( C, D ), probs=(1:n.C-0.5)/n.C )
> A.pt <- sort( A[match( unique(A), A )] )
> P.pt <- sort( P[match( unique(P), P )] )
> C.pt <- sort( C[match( unique(C), C )] )
> # Age-cohort model with age-sex interaction
> # The model matrices for the ML fit
> # - note that intercept is in age term, and drift is added to the cohort term:
> Ma <- Ns( A, kn=A.kn, intercept=T )
> Mc <- cbind( C-c0, detrend( Ns( C, kn=C.kn ), C, weight=D ) )
```

APC-model: Interactions (APC-Int)

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## APC-model: Interactions

Bendix Carstensen

Statistical Analysis in the  
Lexis Diagram:

Age-Period-Cohort models  
— and some cousins

European Doctoral School of Demography, Odense,  
June 2018

<http://BendixCarstensen/APC/EDSD-2018>

APC-Int

## Analysis of DM-rates: Age×sex interaction IV

```
> Mp <- detrend( Ns( P, kn=P.kn ), P, weight=D )
> # The prediction matrices - corresponding to ordered unique values of A, P and C
> Pa <- Ma[match(A.pt,A),,drop=F]
> Pp <- Mp[match(P.pt,P),,drop=F]
> Pc <- Mc[match(C.pt,C),,drop=F]
> # Fit the apc model using the cohort major parametrization
> apcs <- glm( D ~ Ma:sex - 1 + Mc + Mp +
+           offset( log( Y/10^5 ) ),
+           family=poisson, epsilon = 1e-10,
+           data=dm )
> ci.exp( apcs )
```

APC-model: Interactions (APC-Int)

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## Analysis of DM-rates: Age×sex interaction I

- ▶ 10 centres
  - ▶ 2 sexes
  - ▶ Age: 0–15
  - ▶ Period 1989–1999
- ▶ Is the sex-effect the same between all centres?
- ▶ How is timetrend by birth cohort?

APC-model: Interactions (APC-Int)

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## Analysis of DM-rates: Age×sex interaction V

	exp(Est.)	2.5%	97.5%
Mc	1.0053157	0.9719640	1.0398118
Mc1	0.6496197	0.3305926	1.2765132
Mc2	1.2576228	0.6868926	2.3025652
Mc3	0.5366885	0.2787860	1.0331743
Mc4	0.9207689	0.4877809	1.7381069
Mc5	0.6898805	0.3999550	1.1899714
Mc6	1.1005438	0.5817089	2.0821352
Mp1	0.5735223	0.3489977	0.9424928
Mp2	1.0534148	0.6090201	1.8220792
Mp3	0.9412582	0.4032633	2.1969937
Ma1:sexF	11.9104421	6.7605869	20.9831831
Ma2:sexF	22.0985163	11.9531639	40.8548253
Ma3:sexF	16.5201055	9.6623215	28.2451673
Ma4:sexF	360.8119685	225.4568974	577.4286708
Ma5:sexF	2.5694234	1.5219041	4.3379452
Ma1:sexM	17.0238730	9.9414867	29.1518021
Ma2:sexM	13.4664178	7.0861312	25.5914549
Ma3:sexM	14.4664367	8.6164003	24.2883087

APC-model: Interactions (APC-Int)

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## Analysis of DM-rates: Age×sex interaction II

```
> library( Epi )
> library( splines )
> # load( file="c:/Bendix/Artikler/A_P_C/IDDM/Eurodiab/data/tri.Rdata" )
> load( file = "~/teach/APC/examples/EuroDiab/tri.Rdata" )
> str(dm)

'data.frame': 5940 obs. of 8 variables:
 $ sex: Factor w/ 2 levels "F","M": 1 1 1 1 1 1 1 1 1 ...
 $ cen: Factor w/ 10 levels "Z2: Czech","A1: Austria",...: 2 2 2 2 2 2 2 2 2 ...
 $ per: num 1989 1990 1991 1992 1993 ...
 $ D : num 1 0 0 0 0 0 0 0 0 1 ...
 $ A : num 0.333 0.333 0.333 0.333 0.333 ...
 $ P : num 1990 1991 1992 1993 1994 ...
 $ C : num 1989 1990 1991 1992 1993 ...
 $ Y : num 21970 22740 22886 23026 22323 ...
```

APC-model: Interactions (APC-Int)

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## Analysis of DM-rates: Age×sex interaction VI

```
Ma4:sexM 531.9214375 343.2221445 824.3652694
Ma5:sexM 3.1485499 1.9406858 5.1081770

> # Average trend (D-projection)
> round( ( ci.exp( apcs, subset=1 ) - 1 ) *100, 1 )

exp(Est.) 2.5% 97.5%
Mc 0.5 -2.8 4

> ci.exp( apcs, subset="sexF" )

exp(Est.) 2.5% 97.5%
Ma1:sexF 11.910442 6.760587 20.983183
Ma2:sexF 22.098516 11.953164 40.854825
Ma3:sexF 16.520106 9.662321 28.245167
Ma4:sexF 360.811968 225.456897 577.428671
Ma5:sexF 2.569423 1.521904 4.337945

> cbind( A.pt, ci.exp( apcs, subset="sexF", ctr.mat=Pa ) )
```

APC-model: Interactions (APC-Int)

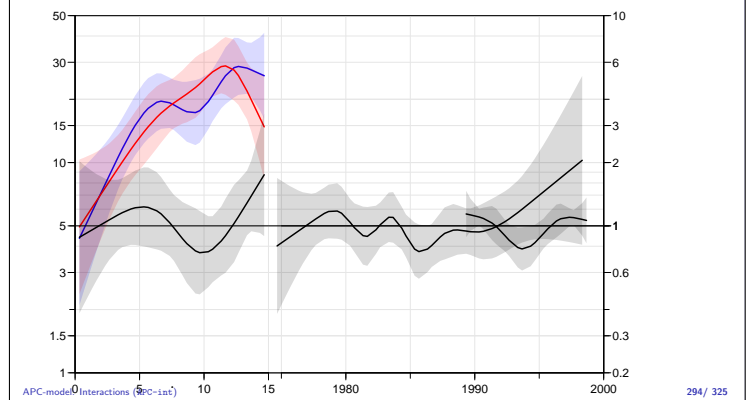
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## Analysis of DM-rates: Age×sex interaction VII

	A.pt	exp(Est.)	2.5%	97.5%
[1,]	0.3333333	4.943285	2.363023	10.34102
[2,]	0.6666667	5.309563	2.676029	10.53481
[3,]	1.3333333	6.125551	3.416160	10.98379
[4,]	1.6666667	6.579431	3.847562	11.25100
[5,]	2.3333333	7.590575	4.833655	11.91993
[6,]	2.6666667	8.153008	5.380890	12.35326
[7,]	3.3333333	9.401089	6.531373	13.53168
[8,]	3.6666667	10.085197	7.103019	14.31943
[9,]	4.3333333	11.561158	8.190634	16.31869
[10,]	4.6666667	12.344483	8.712446	17.49064
[11,]	5.3333333	13.969938	9.777715	19.95959
[12,]	5.6666667	14.794673	10.355375	21.13708
[13,]	6.3333333	16.412682	11.674678	23.07354
[14,]	6.6666667	17.179232	12.425801	23.75107
[15,]	7.3333333	18.578132	13.958075	24.72741
[16,]	7.6666667	19.228123	14.579373	25.35917
[17,]	8.3333333	20.513353	15.309646	27.48579
[18,]	8.6666667	21.190703	15.538953	28.89808

APC-model: Interactions (APC-1st)

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APC-model: Interactions (APC-1st)

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## Analysis of DM-rates: Age×sex interaction VIII

[19,]	9.3333333	22.742587	16.317839	31.69692
[20,]	9.6666667	23.679333	17.100960	32.78827
[21,]	10.3333333	25.893547	19.499950	34.38346
[22,]	10.6666667	26.999519	20.607727	35.37382
[23,]	11.3333333	28.605296	21.348779	38.32832
[24,]	11.6666667	28.831963	21.013988	39.55851
[25,]	12.3333333	27.526786	19.701501	38.46022
[26,]	12.6666667	25.941507	18.827598	35.74337
[27,]	13.3333333	21.900696	16.035816	29.91058
[28,]	13.6666667	19.869417	14.038380	28.12246
[29,]	14.3333333	16.320075	10.026866	26.56312
[30,]	14.6666667	14.790766	8.323640	26.28258

```

> # Extract the effects
> F.inc <- ci.exp( apcs, subset="sexF", ctr.mat=Pa)
> M.inc <- ci.exp( apcs, subset="sexM", ctr.mat=Pa)
> MF.RR <- ci.exp( apcs, subset=c("sexM","sexF"), ctr.mat=cbind(Pa,-Pa))
> c.RR <- ci.exp( apcs, subset="Mc", ctr.mat=Pc)
> p.RR <- ci.exp( apcs, subset="Mp", ctr.mat=Pp)

```

APC-model: Interactions (APC-1st)

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## Analysis of DM-rates: Age×sex interaction I

A bit more intuitive, independent of parametrization:

```

> apcS <- glm( D ~ Ns(A,knots=A.kn,intercept=TRUE):sex +
+             Ns(P,knots=P.kn) + Ns(C,knots=C.kn) +
+             offset( log( Y/10^5 ) ),
+             family=poisson, epsilon = 1e-10,
+             data=dm )
> apcS$deviance
[1] 633.5838
> apcs$deviance
[1] 633.5838

```

APC-model: Interactions (APC-1st)

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## Analysis of DM-rates: Age×sex interaction IX

The the frame for the effects

```

> par( mar=c(4,4,1,4), mgp=c(3,1,0)/1.6, las=1 )
> apc.frame( a.lab=c(0,5,10,15),
+           a.tic=c(0,5,10,15),
+           r.lab=c(c(1,1.5,3,5),c(1,1.5,3,5)*10),
+           r.tic=c(c(1,1.5,2,5),c(1,1.5,2,5)*10),
+           cp.lab=seq(1980,2000,10),
+           cp.tic=seq(1975,2000,5),
+           rr.ref=5,
+           gap=1,
+           col.grid=gray(0.9),
+           a.txt="",
+           cp.txt="",
+           r.txt="",
+           rr.txt="" )
> ###
> ### Draw the estimates
> ###

```

APC-model: Interactions (APC-1st)

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## Analysis of DM-rates: Age×sex interaction II

```

> # rates for the 1985 birth cohort and the RR
> a.pt <- seq(0,15,0.1)
> ndaM <- data.frame( A=a.pt, P=1985+a.pt, C=1985, Y=10^5, sex="M" )
> ndaF <- data.frame( A=a.pt, P=1985+a.pt, C=1985, Y=10^5, sex="F" )
> a.pM <- ci.pred( apcS, ndaM )
> a.pF <- ci.pred( apcS, ndaF )
> a.RR <- ci.exp( apcS, list(ndaM,ndaF) )
> # Cohort RRs relative to C=1985
> ndc <- data.frame( A=10, P=2000, C=1975:2000, Y=10^5 )
> ndr <- data.frame( A=10, P=2000, C=1985, Y=10^5 )
> c.RR <- ci.exp( apcS, list(ndc,ndr) )
> # Period RRs relative to P=2000
> ndp <- data.frame( A=10, P=1990:2000, C=1985, Y=10^5 )
> ndr <- data.frame( A=10, P=2000, C=1985, Y=10^5 )
> p.RR <- ci.exp( apcS, list(ndp,ndr) )
> # plt( paste( "DM-DK" ), width=11 )
> par( mar=c(4,4,1,4), mgp=c(3,1,0)/1.6, las=1 )
> #
> # The the frame for the effects

```

APC-model: Interactions (APC-1st)

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## Analysis of DM-rates: Age×sex interaction X

```

> matshade( A.pt, M.inc, lwd=2, col="blue" )
> matshade( A.pt, F.inc, lwd=2, col="red" )
> matshade( A.pt, MF.RR*5, lwd=2 ) ; abline( h=5 )
> pc.matshade( C.pt, c.RR, lwd=2 )
> pc.matshade( P.pt, p.RR, lwd=2 )

```

APC-model: Interactions (APC-1st)

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## Analysis of DM-rates: Age×sex interaction III

```

> apc.frame( a.lab=c(0,5,10,15),
+           a.tic=c(0,5,10,15),
+           r.lab=c(c(1,1.5,3,5),c(1,1.5,3,5)*10),
+           r.tic=c(c(1,1.5,2,5),c(1,1.5,2,5)*10),
+           cp.lab=seq(1980,2000,10),
+           cp.tic=seq(1975,2000,5),
+           rr.ref=5,
+           gap=1,
+           col.grid=gray(0.9),
+           a.txt="",
+           cp.txt="",
+           r.txt="",
+           rr.txt="" )
> # Draw the estimates
> matshade( a.pt, a.pM, lwd=2, col="blue" )
> matshade( a.pt, a.pF, lwd=2, col="red" )
> matshade( a.pt, a.RR*5, lwd=2 ) ; abline( h=5 )
> pc.matshade( 1975:2000, c.RR, lwd=2 )
> pc.matshade( 1990:2000, p.RR, lwd=2 )

```

APC-model: Interactions (APC-1st)

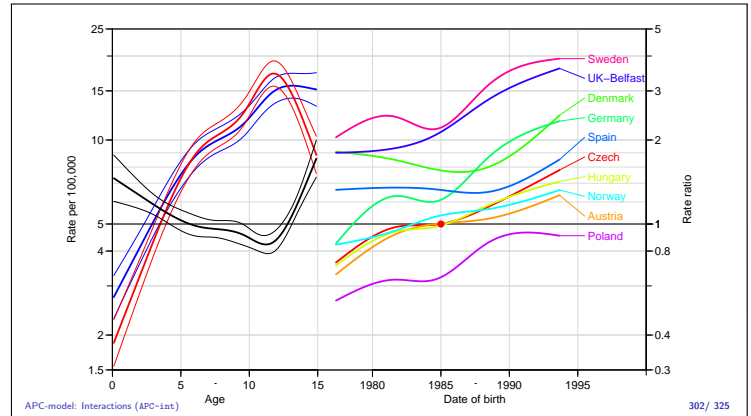
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## Analysis of DM-rates: Age×sex interaction IV

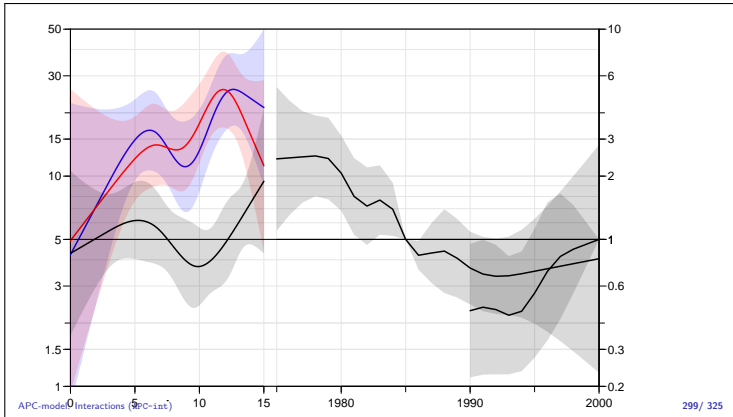
APC-model: Interactions (APC-1st)

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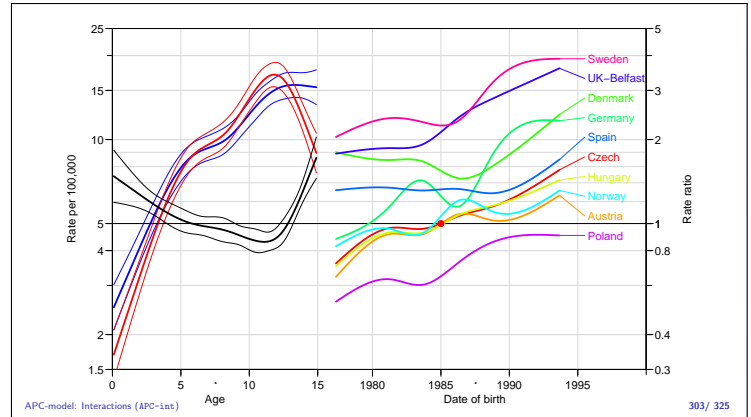
APC-model: Interactions (APC-1st)

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APC-model: Interactions (APC-1st)

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APC-model: Interactions (APC-1st)

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- ▶ ... but these are not the estimates we really want as before.
- ▶ The detrended estimates are not available from the fitted values, because the parametrization they rely on is a function of **data**.
- ▶ Of course the parameters can be extracted but it requires a construction of the model matrices as we did first
- ▶ How is shown in the section "Reparametrizations" in the notes on "Introductory linear algebra with R".

APC-model: Interactions (APC-1st)

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## Predicting future rates

**Bendix Carstensen**

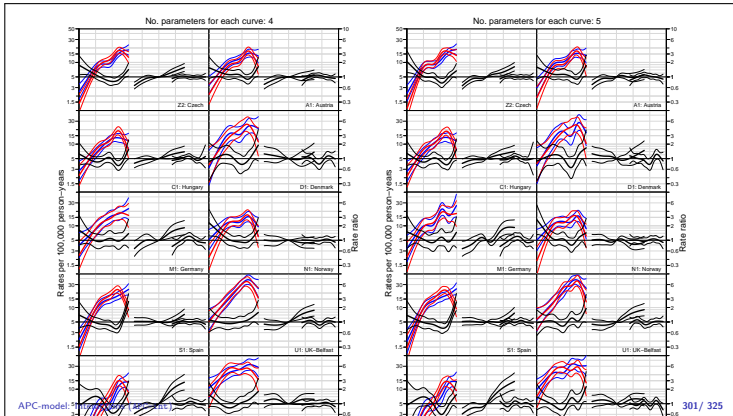
Statistical Analysis in the Lexis Diagram:

Age-Period-Cohort models  
— and some cousins

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June 2018

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predict



APC-model: Interactions (APC-1st)

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## Prediction of future rates

Model:

$$\log(\lambda(a, p)) = f(a) + g(p) + h(c)$$

- ▶ Why not just extend the estimated functions into the future?
- ▶ Natural splines lend themselves easily to this [?]
- ▶ The parametrization curse — the model as stated is not uniquely parametrized.
- ▶ Predictions from the model must be invariant under reparametrization.

Predicting future rates (predict)

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## Identifiability

Predictions based in the three functions  $(f(a), g(p)$  and  $h(c)$  must give the same prediction also for the reparametrized version:

$$\begin{aligned}\log(\lambda(a, p)) &= \tilde{f}(a) + \tilde{g}(p) + \tilde{h}(c) \\ &= (f(a) - \gamma a) + \\ &\quad (g(p) + \gamma p) + \\ &\quad (h(c) - \gamma c)\end{aligned}$$

A prediction based on the parametrization  $(f(a), g(p), h(c))$  must give the same predictions as one based on  $(\tilde{f}(a), \tilde{g}(p), \tilde{h}(c))$

## Practicalities

- ▶ Long term predictions notoriously unstable.
- ▶ Decreasing slopes are possible, the requirement is that at any future point changes in the parametrization should cancel out in the predictions.

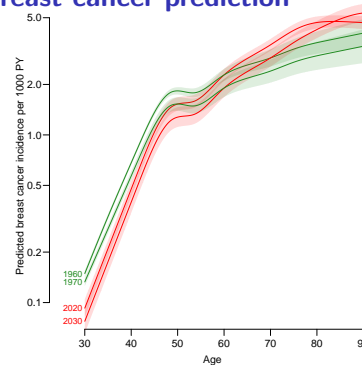
## Parametrization invariance

- ▶ Prediction of the future course of  $g$  and  $h$  must preserve addition of a linear term in the argument:

$$\begin{aligned}\text{pred}(g(p) + \gamma p) &= \text{pred}(g(p)) + \gamma p \\ \text{pred}(h(c) - \gamma c) &= \text{pred}(h(c)) - \gamma c\end{aligned}$$

- ▶ If this is met, the predictions made will not depend on the parametrization chosen.
- ▶ If one of the conditions does not hold, the prediction will depend on the parametrization chosen.
- ▶ Any linear combination of (known) function values of  $g(p)$  and  $h(c)$  will work.

## Breast cancer prediction



Predicted age-specific breast cancer rates at 2020 & 2030,

in the 1960 and 1970 cohorts.

## Identifiability

- ▶ Any linear combination of function values of  $g(p)$  and  $h(c)$  will work.
- ▶ Coefficients in the linear combinations used for  $g$  and  $h$  must be the same; otherwise the prediction will depend on the specific parametrization.
- ▶ What works best in reality is difficult to say: depends on the subject matter.

## Continuous outcomes

### Bendix Carstensen

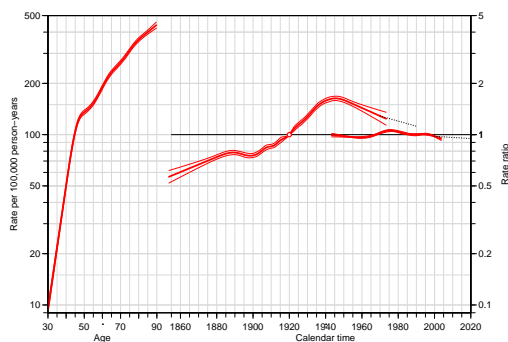
Statistical Analysis in the Lexis Diagram:

Age-Period-Cohort models  
— and some cousins

European Doctoral School of Demography, Odense,  
June 2018

<http://BendixCarstensen/APC/EDSD-2018>

## Example: Breast cancer in Denmark



## APC-model for quantitative outcomes

- ▶ The classical model is:

$$\log(\lambda(a, p)) = f(a) + g(p) + h(p - a)$$

- ▶ In principle it would be possible to use an identity-link model:

$$\lambda(a, p) = f(a) + g(p) + h(p - a)$$

- ▶ ... or use APC-modelling for **measurement** data such as BMI, measured at different times and ages:

$$\text{BMI}_{ap} = f(a) + g(p) + h(p - a) + e_{ap}, \quad e_i \sim \mathcal{N}(0, \sigma^2)$$

- ▶ ... or more precisely:

$$\text{BMI}_i = f(a(i)) + g(p(i)) + h(p(i) - a(i)) + e_i, \quad e_i \sim \mathcal{N}(0, \sigma^2)$$

## APC-model for quantitative outcomes

- ▶ Model:

$$\text{BMI}_i = f(a(i)) + g(p(i)) + h(p(i) - a(i)) + e_i, \quad e_i \sim \mathcal{N}(0, \sigma^2)$$

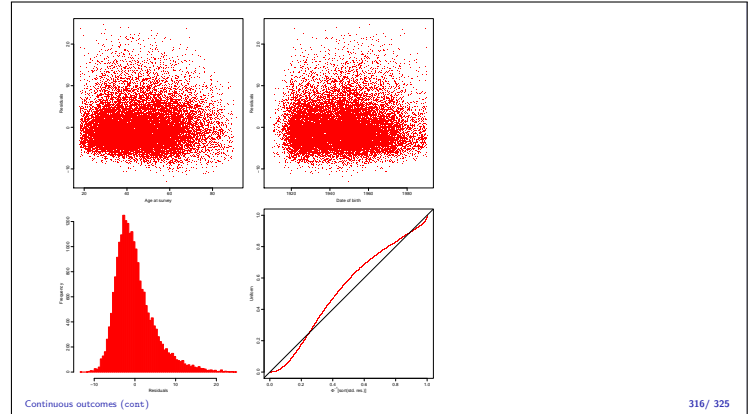
- ▶ But the identification problem is still the same:

$$c(i) = p(i) - a(i), \quad \forall i$$

- ▶ But the same machinery applies with extraction of the effects
- ▶ — and plotting of predictions of
  - ▶ E(BMI)
  - ▶ quantiles of BMI

Continuous outcomes (cont)

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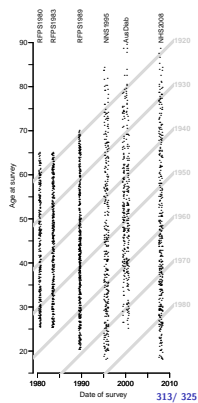


Continuous outcomes (cont)

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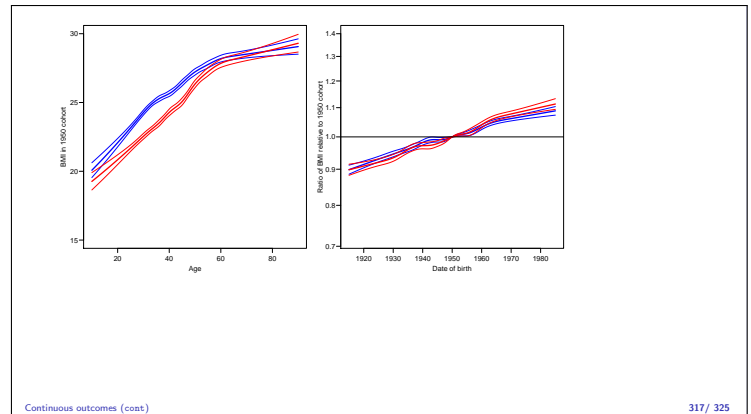
## APC-model for quantitative outcomes

- ▶ Australian surveys
- ▶ 40,000+ person surveyed at different times
- ▶ Date of birth, data of survey, sex and BMI known.
- ▶ How does BMI evolve in the population?
- ▶ Linear model (E(BMI))
- ▶ Quantile regression (median, quantile)
- ▶ — the latter is not a model



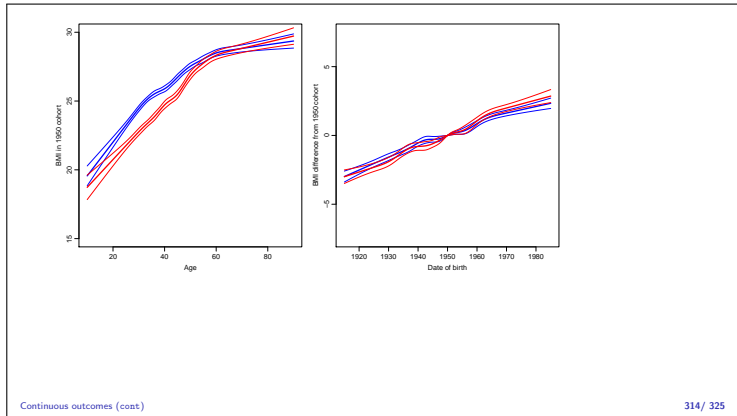
Continuous outcomes (cont)

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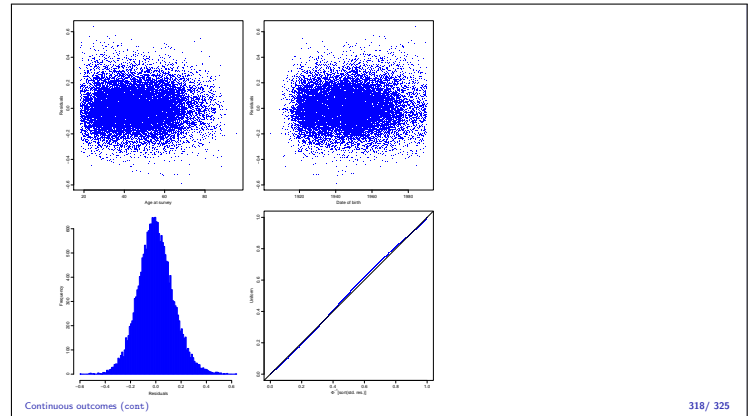
Continuous outcomes (cont)

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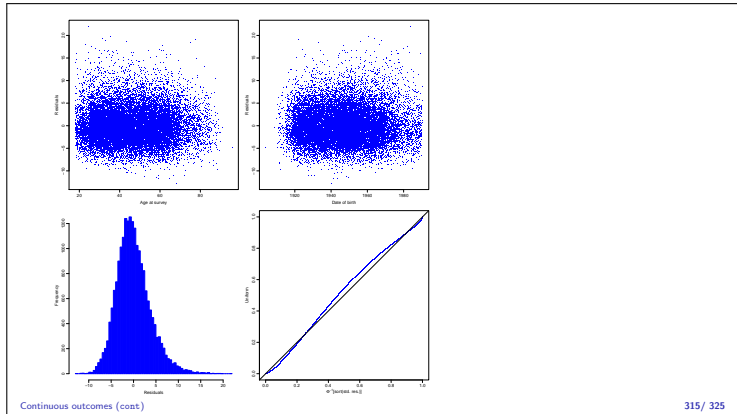
Continuous outcomes (cont)

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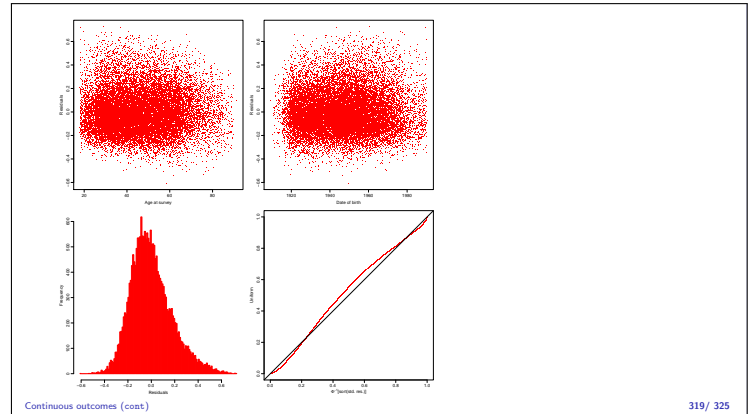
Continuous outcomes (cont)

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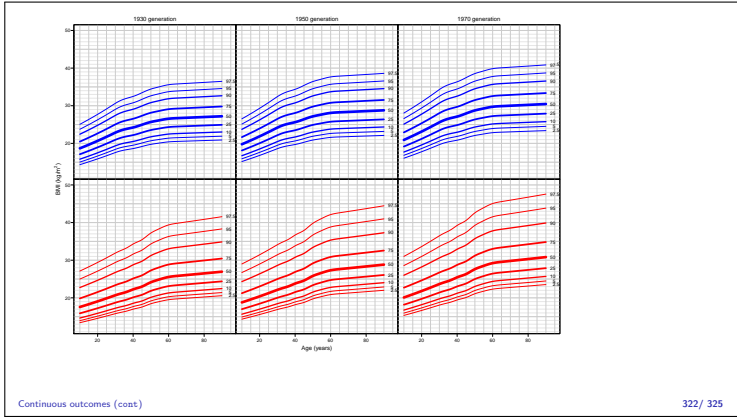
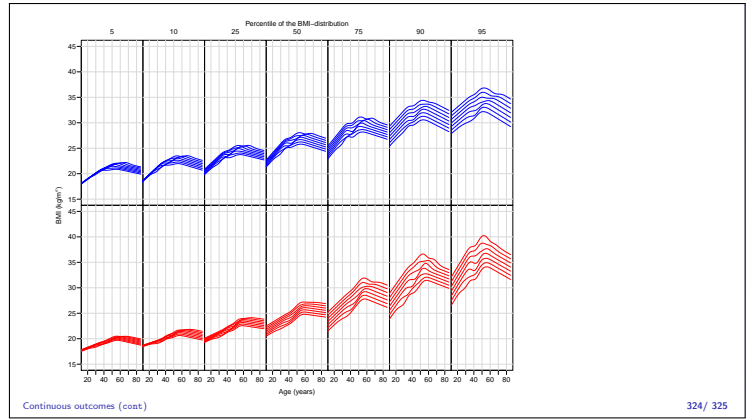
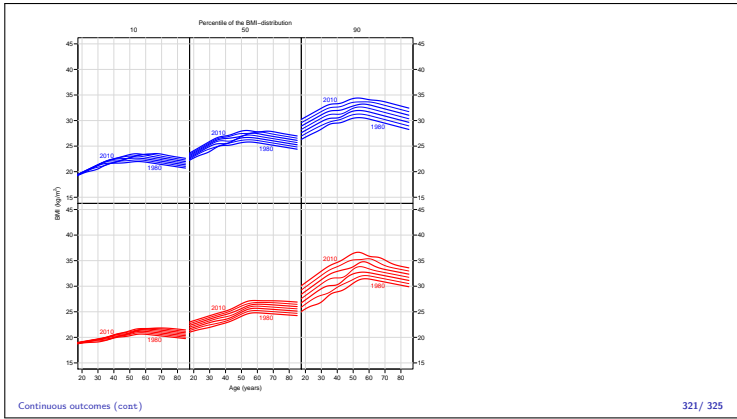
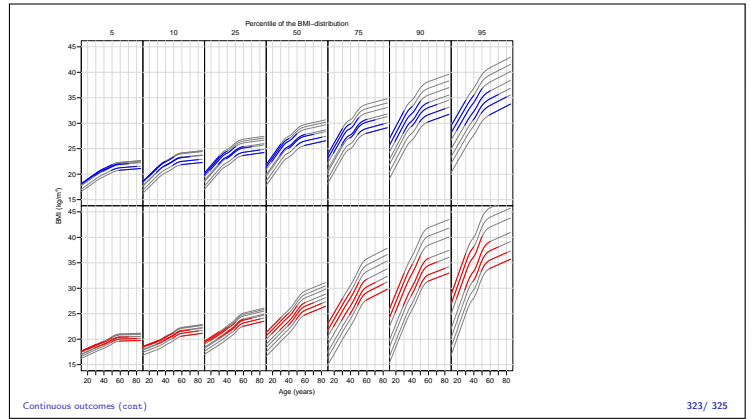
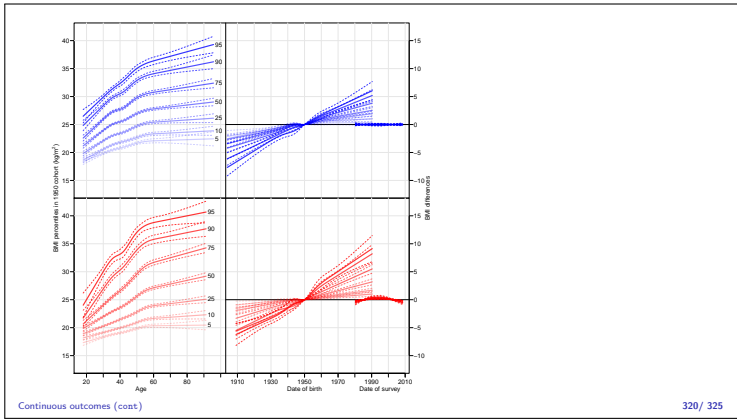
Continuous outcomes (cont)

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Continuous outcomes (cont)

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## References