Statistical Analysis in the Lexis Diagram:

Age-Period-Cohort models

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http://BendixCarstensen/APC/MPIDR-2016

Introduction

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intro

Welcome

- Purpose of the course:
  - knowledge about APC-models
  - technincal knowledge of handling them
  - insight in the basic concepts of survival analysis
- Remedies of the course:
  - Lectures with handouts (BxC)
  - Practicals with suggested solutions (BxC)
  - Asssignment for Thursday

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 in analysis of rates and survival"
  — read it.

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.
- There is a time-schedule in the practicals.
  It might need revision as we go.

About the practicals

- You should use you preferred **R**-enviroment.
- `Epi`-package for **R** is needed.
- Data are all on my 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.
- An opportunity to learn `emacs`, `ESS` and `Sweave`?

Rates and Survival

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surv-rate

Survival data

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

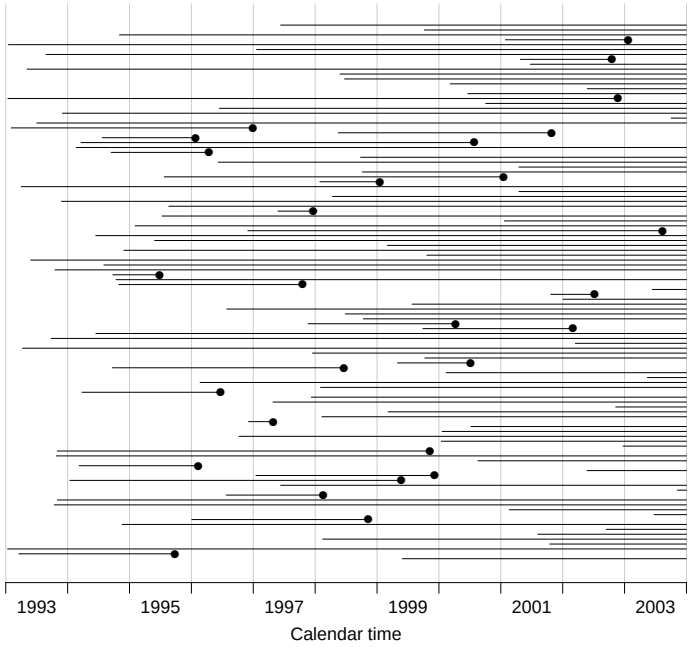
Examples of time-to-event measurements

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

Each line a person

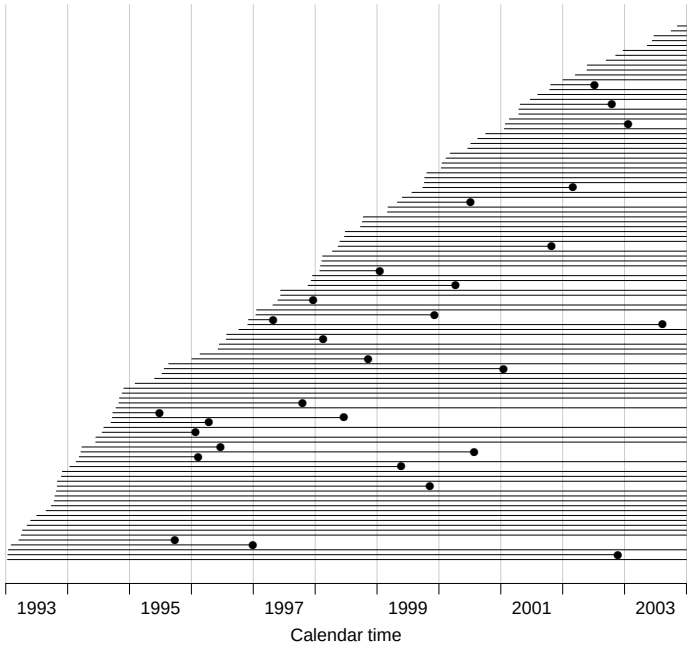
Each blob a death

Study ended at 31 Dec. 2003

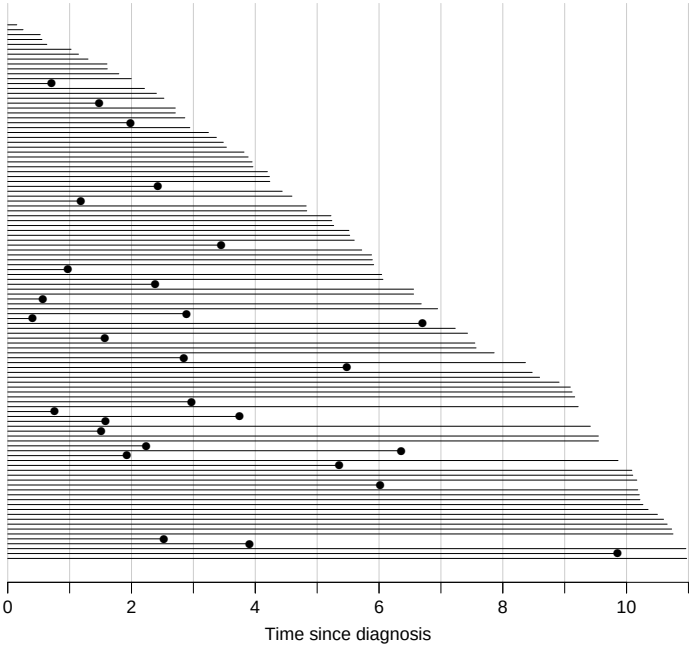


Ordered by date of entry

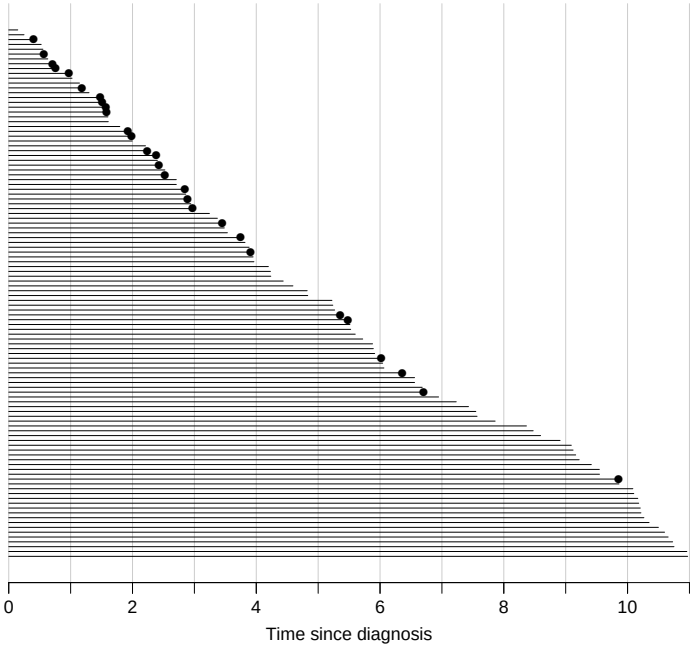
Most likely the order in your database.



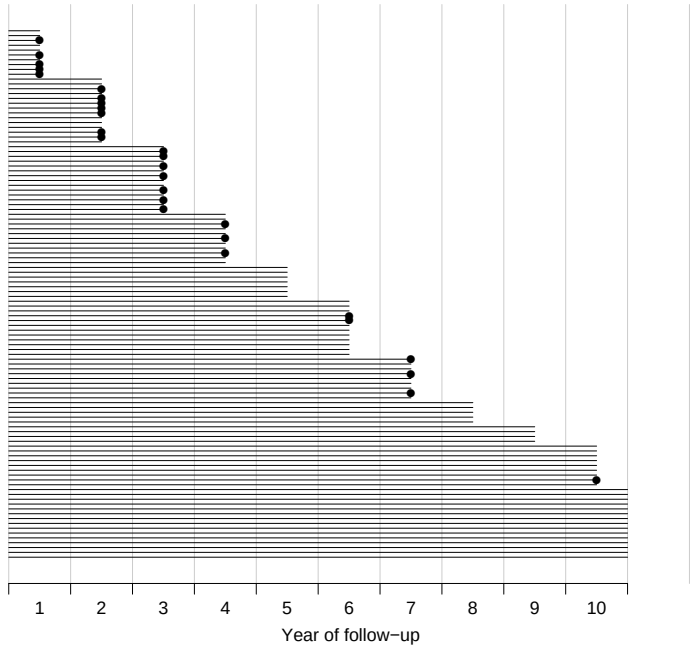
Timescale changed to "Time since diagnosis".



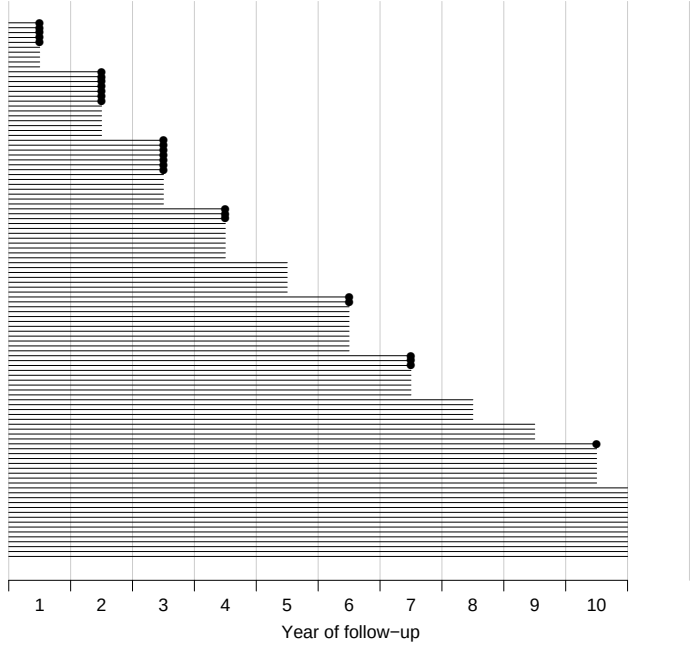
Patients ordered by survival time.



Survival times grouped into bands of survival.



Patients ordered by survival status within each band.



Survival after Cervix cancer

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

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

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

Survival function

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

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

Distribution is characterized by the survival function:

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

Intensity or rate

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

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

Characterizes the survival distribution as does f or F.

Theoretical counterpart of a **rate**.

Relationships

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

$\Lambda(t) = \int_0^t \lambda(s)\,\mathrm{d}s$ is called the **integrated intensity** or **cumulative hazard**.

$\Lambda(t)$ is **not** an intensity — it is dimensionless.

Rate and survival

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

- Survival is a **cumulative** measure
- A rate is an **instantaneous** measure.
- **Note:** A cumulative measure requires an origin!

Observed survival and rate

- Survival studies:
  Observation of (right censored) survival time:

  $$X = \min(T, Z), \qquad \delta = 1\{X = T\}$$

  — sometimes conditional on $T > t_0$, (left truncated).
- Epidemiological studies:
  Observation of (components of) a rate:

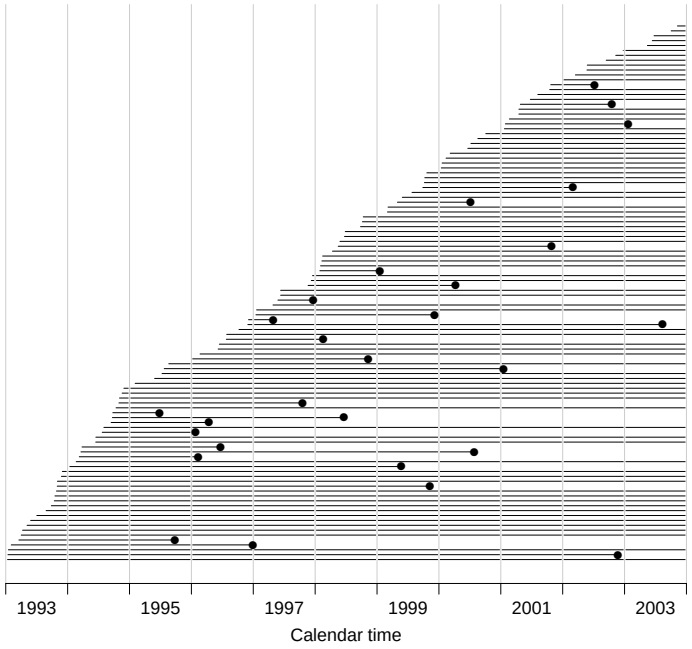
  $$D, \qquad Y, \qquad D/Y$$

  D: no. events, Y no of person-years.

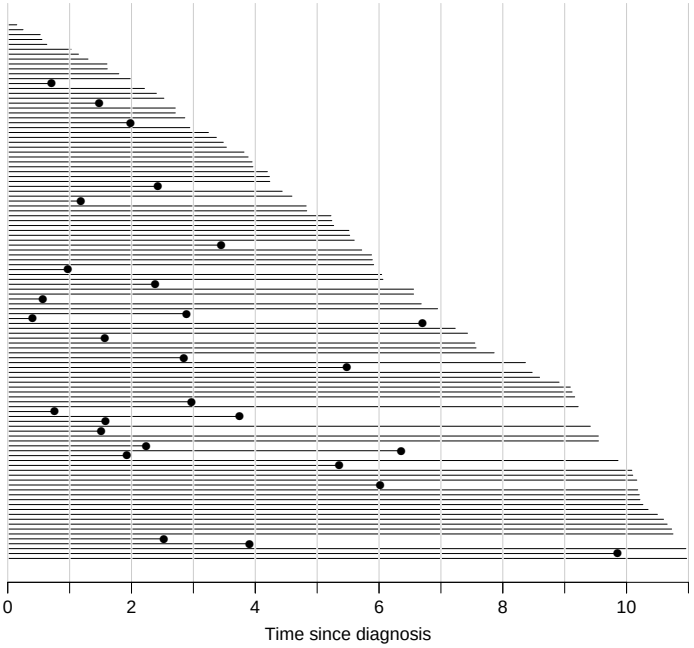
Empirical rates for individuals

- 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**:
  — varies across empirical rates from one individual:
  Age, calendar time, time since diagnosis
- Do not confuse timescale with
  y — risk time (exposure in demograpy)
  a **difference** between two points on **any** timescale

Empirical rates by calendar time.



Empirical rates by time since diagnosis.



Two timescales

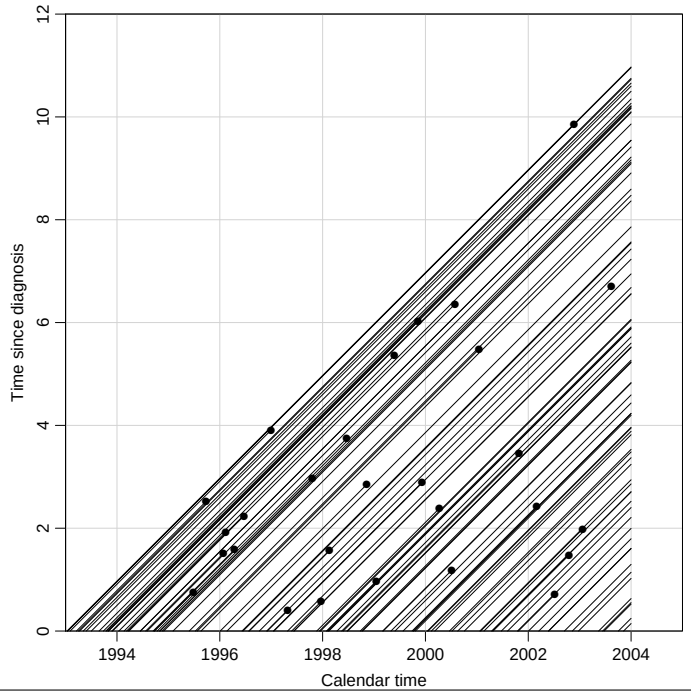
Note that we actually have two timescales:

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

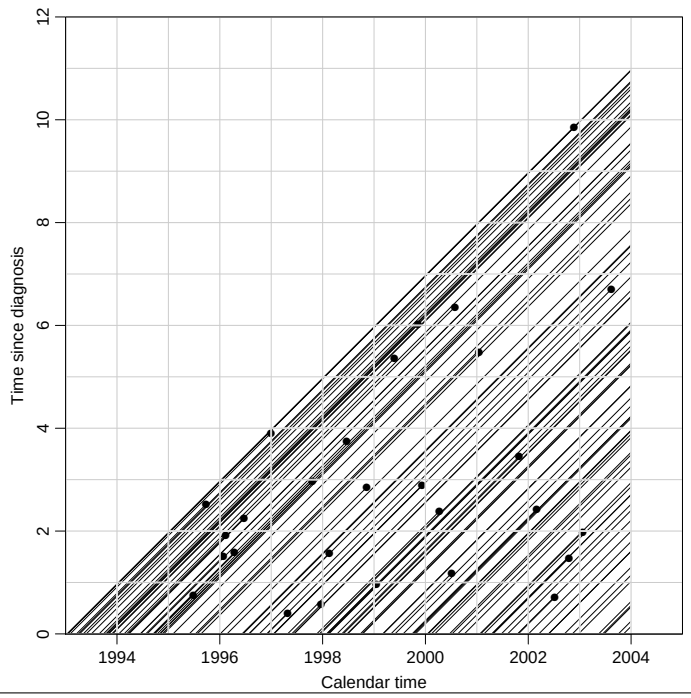
These can be shown simultaneously in a Lexis diagram.

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

A Lexis diagram!



Empirical rates by calendar time *and* time since diagnosis



Likelihood for rates

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`likelihood`

Likelihood contribution from one person

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

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

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

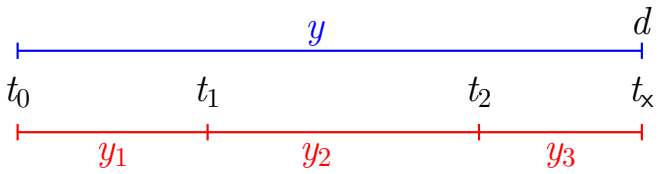
Each term refers to one empirical rate (d, y)
— $y = t_i - t_{i-1}$ (mostly $d = 0$).

Likelihood for an empirical rate

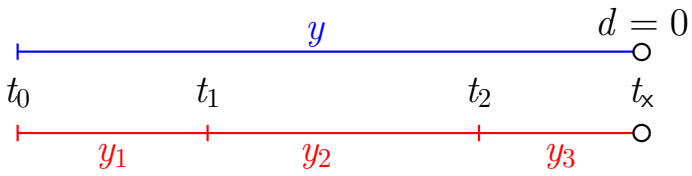
- Likelihood depends on **data** and the **model**
- Model: the rate is constant in the interval.
- The interval should sufficiently small for this assumption to be reasonable.

$$\begin{aligned}L(\lambda(|y, d) &= \mathrm{P}\left\{\text{survive } y\right\} \times \mathrm{P}\left\{\text{event}\right\}^d \\ &= \mathrm{e}^{-\lambda y} \times (\lambda\,\mathrm{d}t)^d \\ &= \lambda^d \mathrm{e}^{-\lambda y}\end{aligned}$$

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



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



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$\mathrm{P}(\text{surv } t_0 \to t_x \mid \text{entry } t_0)$	$0\log(\lambda) - \lambda y$
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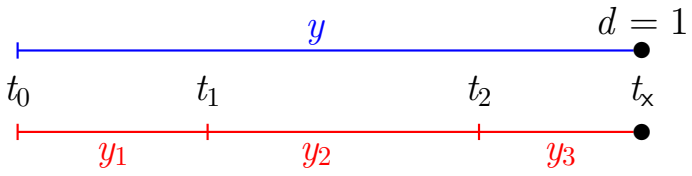


Probability	log-Likelihood
$\mathrm{P}(\text{event at } t_x \mid \text{entry } t_0)$	$1\log(\lambda) - \lambda y$
$= \mathrm{P}(\text{surv } t_0 \to t_1 \mid \text{entry } t_0)$	$= 0\log(\lambda) - \lambda y_1$
$\times \mathrm{P}(\text{surv } t_1 \to t_2 \mid \text{entry } t_1)$	$+ 0\log(\lambda) - \lambda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

Aim of dividing time into bands:

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

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

Log-likelihood from more persons

- One person, p: $\sum_t \left(d_{pt}\log(\lambda_t) - \lambda_t y_{pt}\right)$
- More persons: $\sum_p \sum_t \left(d_{pt}\log(\lambda_t) - \lambda_t y_{pt}\right)$
- Collect terms with identical values of λ_t:

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

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

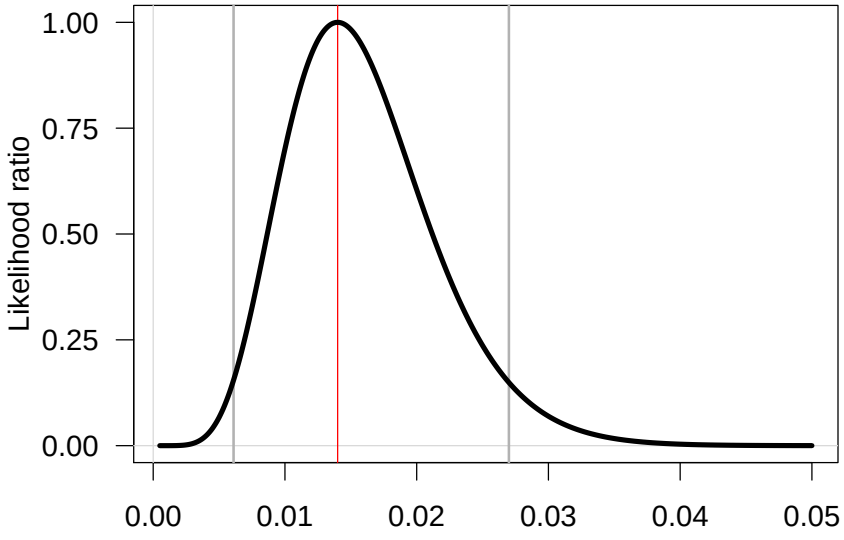
Likelihood example

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

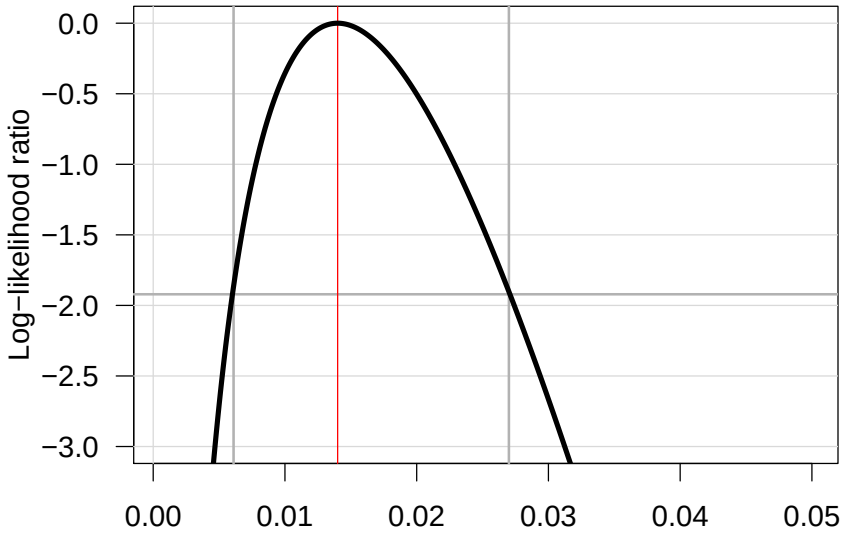
$$\begin{aligned} \mathrm{P}\left\{D = 7, Y = 500|\lambda\right\} &= \lambda^D \mathrm{e}^{\lambda Y} \times K \\ &= \lambda^7 \mathrm{e}^{\lambda 500} \times K \\ &= L(\lambda|\text{data}) \end{aligned}$$

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

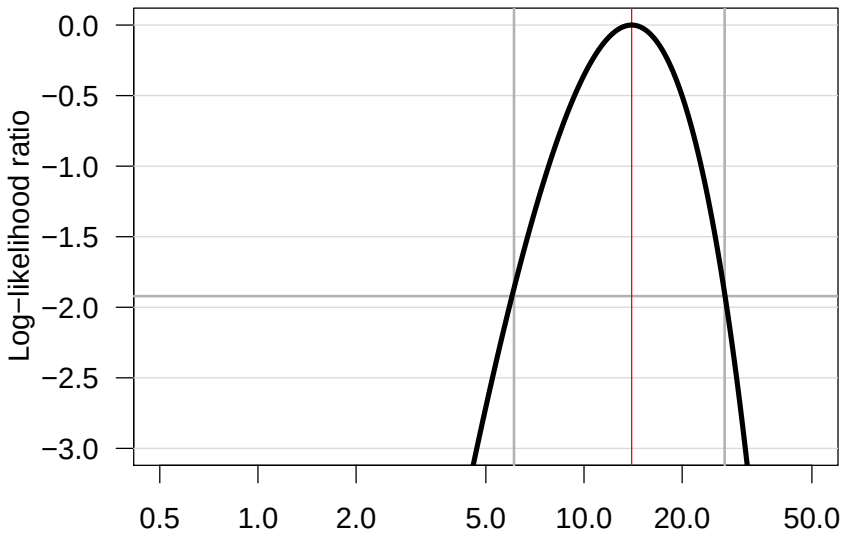
Likelihood-ratio function



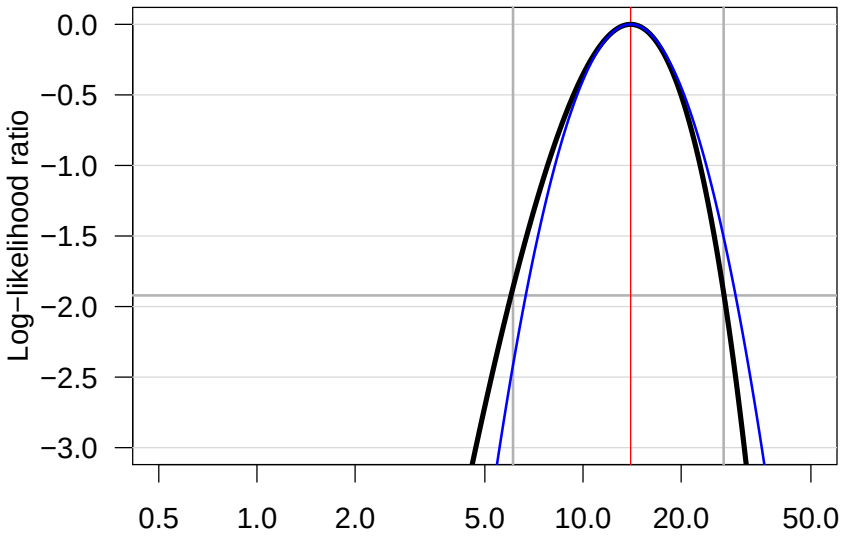
Log-likelihood ratio



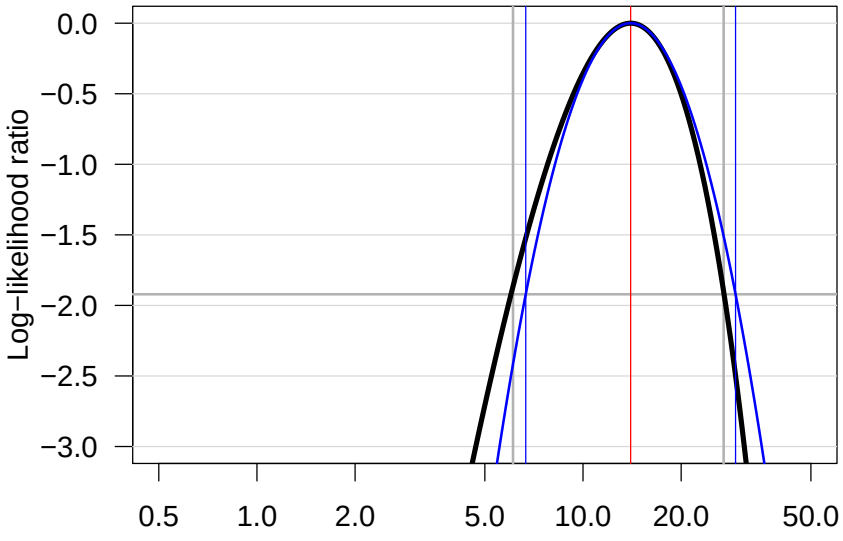
Log-likelihood ratio



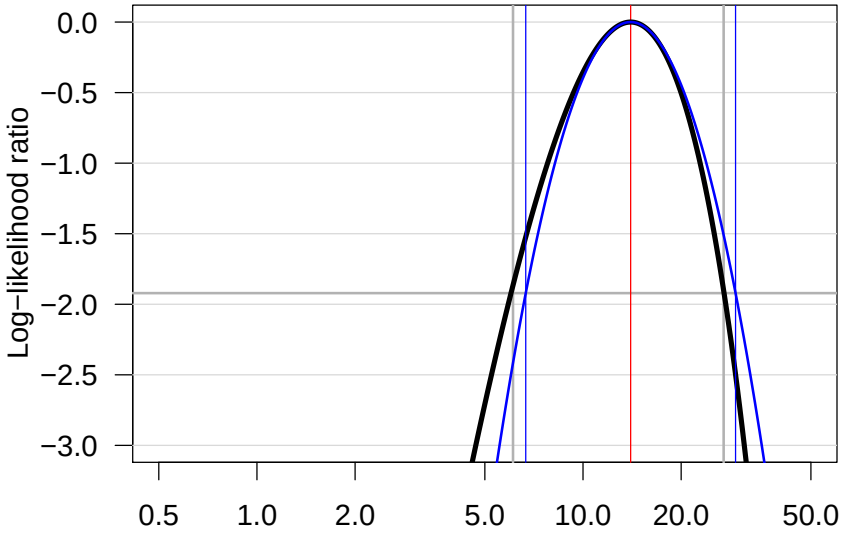
Log-likelihood ratio



Log-likelihood ratio



Log-likelihood ratio



$\hat{\lambda} = 7/500 = 14$

$\hat{\lambda} \stackrel{\times}{\div} \exp(1.96/\sqrt{7}) = (6.7, 29.4)$

Poisson likelihood

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

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

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

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

Extra term does not depend on the rate parameter λ.

Poisson likelihood

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

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

- Terms 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 $\mu = \lambda_t y_{py} \Leftrightarrow \log\mu = \log(\lambda_t) + \log(y_{py})$

$\Rightarrow$ Analyse rates λ based on empirical rates (d,y) Poisson model with log-link applied to where:

- d is the response variable.
- $\log(y)$ is the offset variable.

Likelihood for follow-up of many subjects

Adding empirical rates over the follow-up of persons:

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

- Persons are assumed independent
- Contribution from the same person are *conditionally* independent, hence give separate contributions to the log-likelihood.

The log-likelihood is maximal for:

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

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

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

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

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

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

The log-likelihood is maximal for:

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

Information about the rate itself, λ:

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

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

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

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:

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

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

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

Exercise

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

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

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
```


Ratio of two rates

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

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

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

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

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.

Lifetables

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lifetable

The life table method

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

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

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

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 $(n_i - d_i/2 - l_i/2) \times \ell_i$:

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

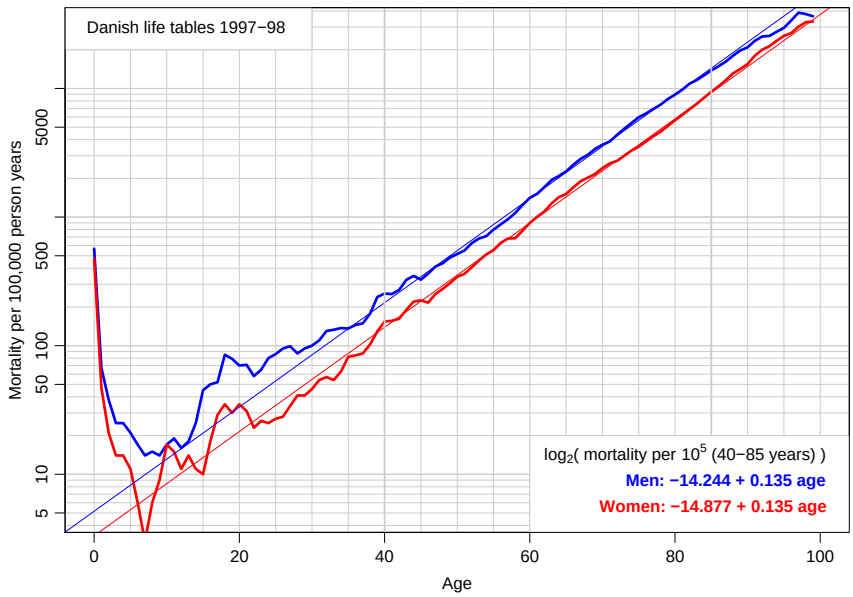
and hence the death probability:

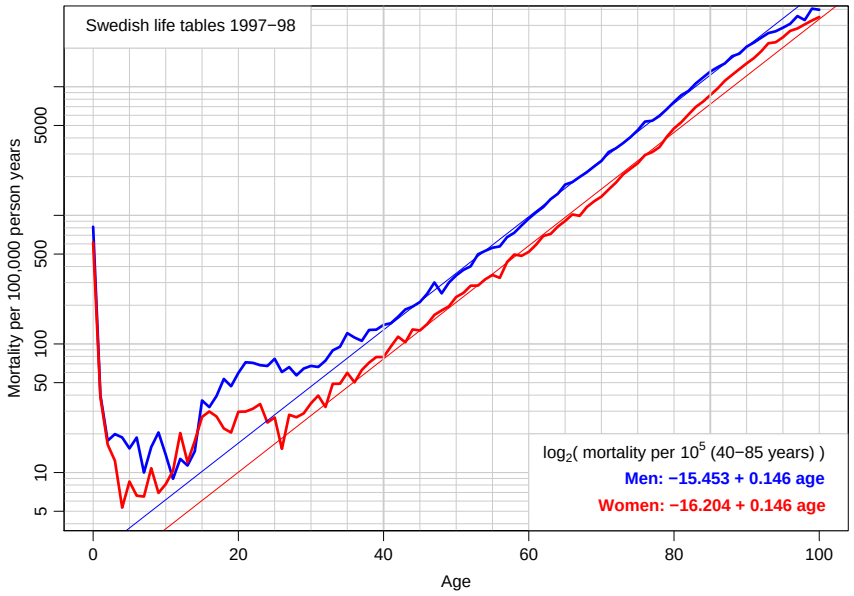
$$p_i = 1 - \exp -\lambda_i \ell_i = 1 - \exp\left(-\frac{d_i}{(n_i - d_i/2 - l_i/2)}\right)$$

The modified life-table estimator.

Population life table, DK 1997–98

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





Practical

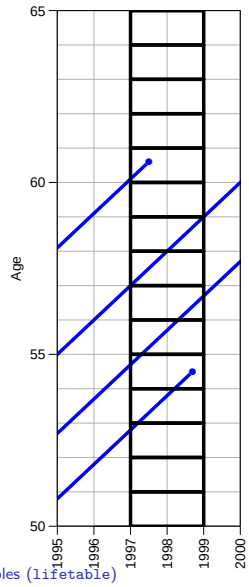
Based on the previous slides answer the following for both Danish and Swedish lifetables:

- 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?

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

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

Observations for the lifetable



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

Age-specific rates — cross-sectional!

Survival function:

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

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

Life table approach

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

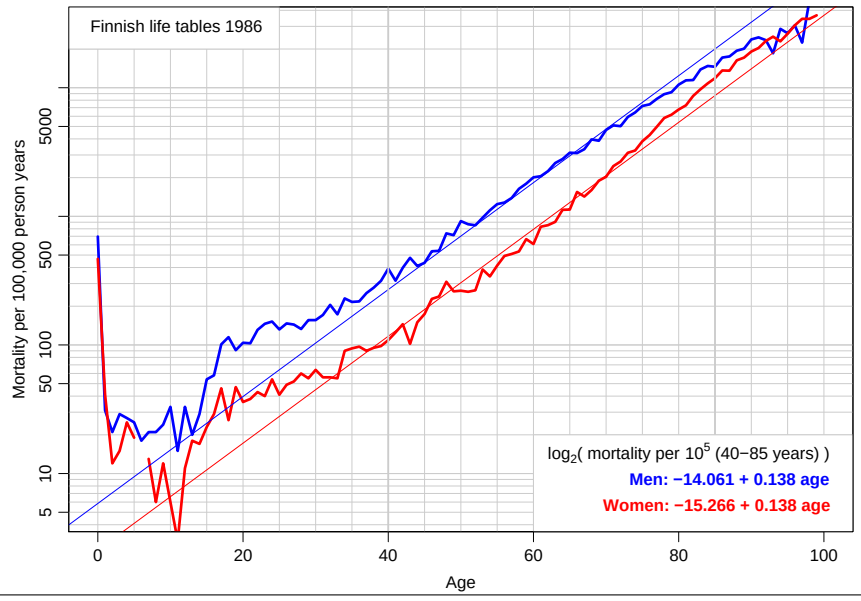
It is the **population** experience:

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

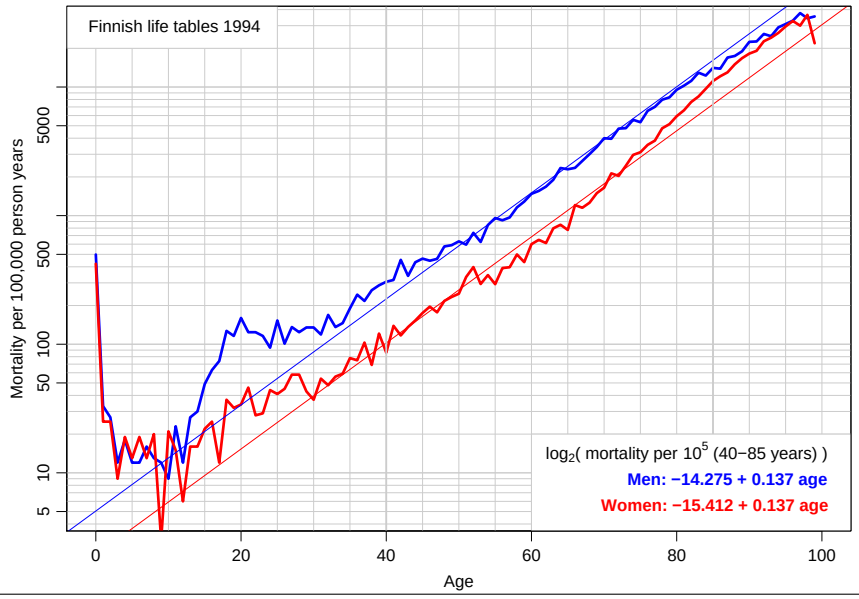
The classical lifetable analysis compiles these for prespecified intervals of age, and computes age-specific mortality **rates**.

Data are collected cross-sectionally, but interpreted longitudinally.

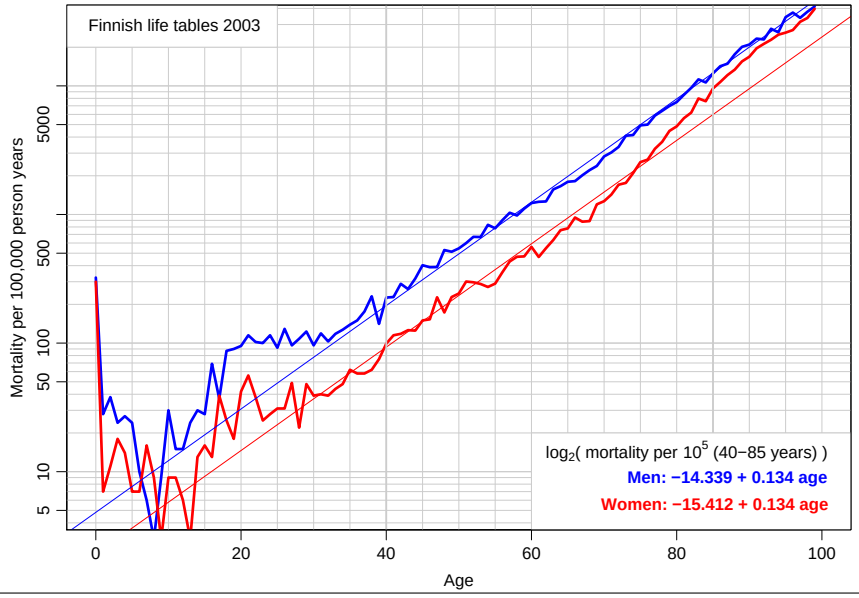
Rates vary over time:



Rates vary over time:



Rates vary over time:



Who needs the Cox-model anyway?

Statistical Analysis in the
Lexis Diagram:

Age-Period-Cohort models
May 2016
Max Planck Institut for Demographic Research, Rostock
http://BendixCarstensen/APC/MPIDR-2016

WntCma

A look at the Cox model

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

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

The covariate t has a special status:

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

Cox-likelihood

The (partial) log-likelihood for the regression parameters:

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

is also a **profile likelihood** in the model where observation time has been subdivided in small pieces (empirical rates) and each small piece provided with its own parameter:

$$\log\big(\lambda(t, x)\big) = \log\big(\lambda_0(t)\big) + x'\beta = \alpha_t + \eta$$

The Cox-likelihood as profile likelihood

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

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

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

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

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

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

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

The derivative w.r.t. α_t is:

$$\mathrm{D}_{\alpha_t} \ell(\alpha_t, \beta) = 1 - \mathrm{e}^{\alpha}_t \sum_{i \in \mathcal{R}_t} \mathrm{e}^{\eta_i} = 0 \quad \Leftrightarrow \quad \mathrm{e}^{\alpha}_t = \frac{1}{\sum_{i \in \mathcal{R}_t} \mathrm{e}^{\eta_i}}$$

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

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

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

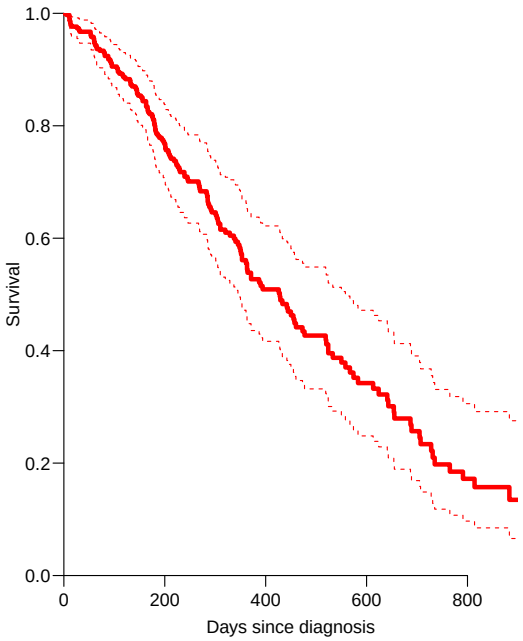
Splitting the dataset

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — much larger than the original dataset
- — 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
  - Covariate value for the timescale (time since entry, current age, current date, ...)
  - other covariates
- Modelling is by standard `glm` Poisson

Example: Mayo Clinic lung cancer

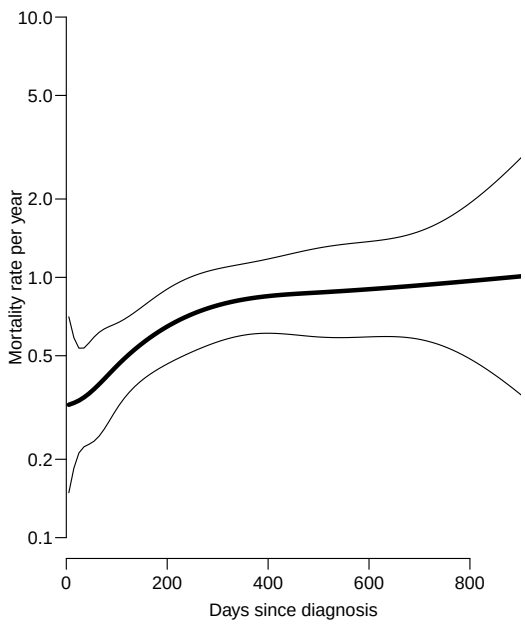
- Survival after lung cancer
- Covariates:
  - Age at diagnosis
  - Sex
  - Time since diagnosis
- Cox model
- Split data:
  - Poisson model, time as factor
  - Poisson model, time as spline

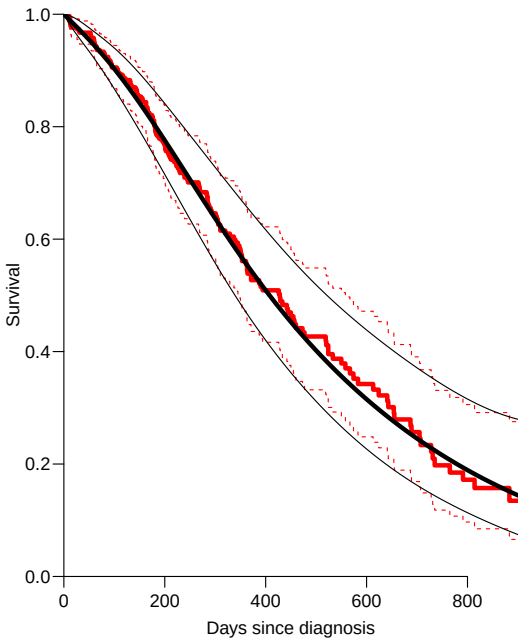
Mayo Clinic lung cancer 60 year old woman

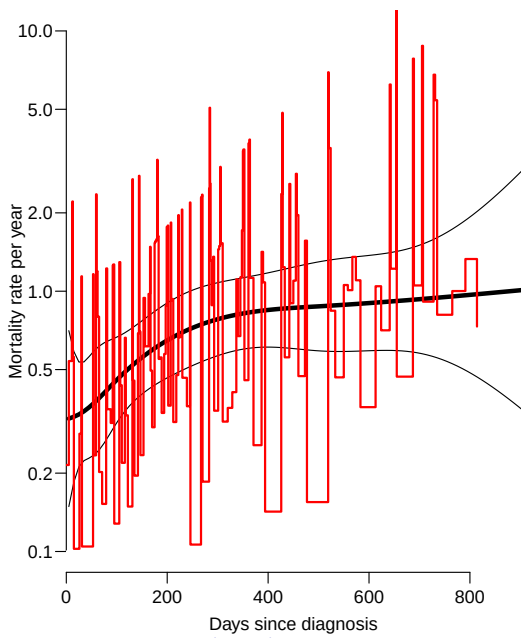


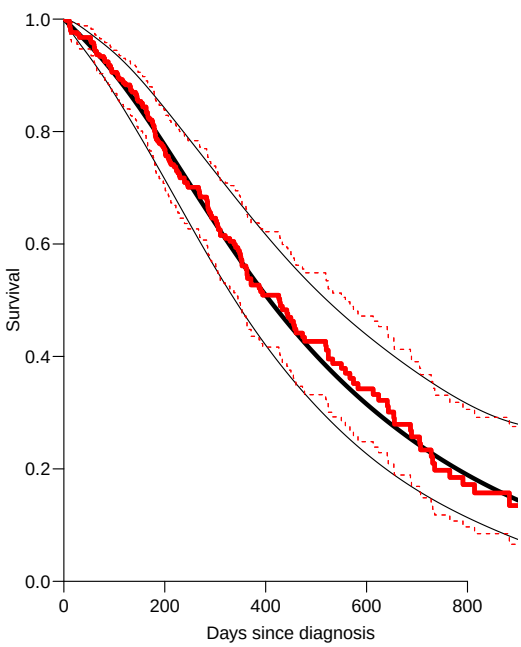
Example: Mayo Clinic lung cancer I

```
> round( cmp, 5 )

                     age    2.5%   97.5%     sex    2.5%   97.5%
Cox              1.01716 0.99894 1.03571 0.59896 0.43137 0.83165
Poisson-factor   1.01716 0.99894 1.03571 0.59896 0.43137 0.83165
Poisson-spline   1.01619 0.99803 1.03468 0.59983 0.43199 0.83287
```







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

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


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.
- $\Rightarrow$ difficult to access the baseline hazard.
- $\Rightarrow$ uninitiated tempted to show survival curves where irrelevant

Modeling in this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant
  - Splines (linear, quadratic or cubic)
  - Fractional polynomials
- 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 in calculations of
  - expected residual life time
  - state occupancy probabilities in multistate models
  - ...

The baseline hazard and survival functions

Using a parametric function to model the baseline hazard gives the possibility to plot this with confidence intervals for a given set of covariate values, x_0

The survival function in a multiplicative Poisson model has the form:

$$S(t) = \exp\Big(-\sum_{\tau<t} \exp(g(\tau) + x_0'\gamma)\Big)$$

This is just a non-linear function of the parameters in the model, g and γ. So the variance can be computed using the δ-method.

δ-method for survival function

1. Select timepoints t_i (fairly close).
2. Get estimates of log-rates $f(t_i) = g(t_i) + x_0'\gamma$ for these points:

$$\hat{f}(t_i) = \mathbf{B}\,\hat{\beta}$$

   where β is the total parameter vector in the model.
3. Variance-covariance matrix of $\hat{\beta}$: $\hat{\Sigma}$.
4. Variance-covariance of $\hat{f}(t_i)$: $\mathbf{B}\Sigma\mathbf{B}'$.
5. Transformation to the rates is the coordinate-wise exponential function, with derivative $\operatorname{diag}\big[\exp\big(\hat{f}(t_i)\big)\big]$

6. Variance-covariance matrix of the rates at the points t_i:

$$\operatorname{diag}(\mathrm{e}^{\hat{f}(t_i)})\,\mathbf{B}\,\hat{\Sigma}\,\mathbf{B}'\operatorname{diag}(\mathrm{e}^{\hat{f}(t_i)})'$$

7. Transformation to cumulative hazard (ℓ is interval length):

$$\ell \times \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 \\ 1 & 1 & 1 & 1 & 0 \end{bmatrix} \begin{bmatrix} \mathrm{e}^{\hat{f}(t_1))} \\ \mathrm{e}^{\hat{f}(t_2))} \\ \mathrm{e}^{\hat{f}(t_3))} \\ \mathrm{e}^{\hat{f}(t_4))} \end{bmatrix} = \mathbf{L} \begin{bmatrix} \mathrm{e}^{\hat{f}(t_1))} \\ \mathrm{e}^{\hat{f}(t_2))} \\ \mathrm{e}^{\hat{f}(t_3))} \\ \mathrm{e}^{\hat{f}(t_4))} \end{bmatrix}$$

8. Variance-covariance matrix for the cumulative hazard is:

$$\mathbf{L}\,\mathrm{diag}(\mathrm{e}^{\hat{f}(t_i)})\,\mathbf{B}\,\hat{\Sigma}\,\mathbf{B}'\,\mathrm{diag}(\mathrm{e}^{\hat{f}(t_i)})'\,\mathbf{L}'$$

This is all implemented in the `ci.cum()` function in `Epi`.

Practical: Cox and Poisson modelling

(non)-Linear models: Estimates and predictions

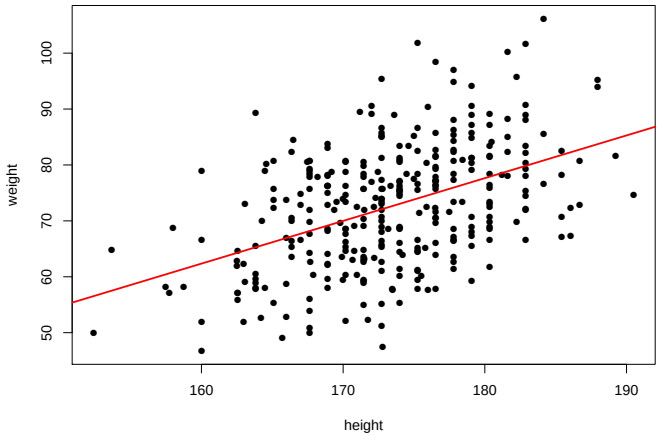
Statistical Analysis in the
Lexis Diagram:

Age-Period-Cohort models
May 2016
Max Planck Institut for Demographic Research, Rostock
http://BendixCarstensen/APC/MPIDR-2016

lin-mod

Linear models

```
> library( Epi )
> data( diet )
> names( diet )

 [1] "id"         "doe"        "dox"        "dob"        "y"          "fail"
 [8] "month"      "energy"     "height"     "weight"     "fat"        "fibre"
[15] "chd"

> with( diet, plot( weight ~ height, pch=16 )  )
> abline( lm( weight ~ height, data=diet ), col="red", lwd=2 )
```

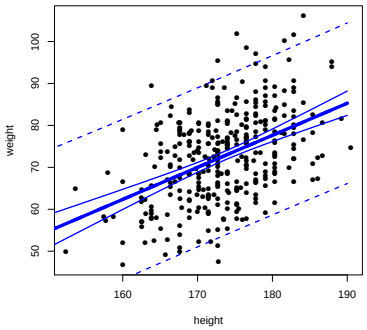



```
> with( diet, plot( weight ~ height, pch=16 )  )
> abline( lm( weight ~ height, data=diet ), col="red", lwd=2 )
```


Linear models, extracting estimates

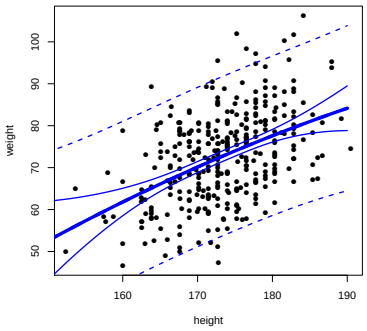
```
> ml <- lm( weight ~ height, data=diet )
> summary( ml )

Call:
lm(formula = weight ~ height, data = diet)

Residuals:
     Min       1Q   Median       3Q      Max
-24.7361  -7.4553   0.1608   6.9384  27.8130

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept) -59.91601   14.31557  -4.185 3.66e-05
height        0.76421    0.08252   9.261  < 2e-16

Residual standard error: 9.625 on 330 degrees of freedom
  (5 observations deleted due to missingness)
Multiple R-squared:  0.2063, Adjusted R-squared:  0.2039
F-statistic: 85.76 on 1 and 330 DF,  p-value: < 2.2e-16

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


Linear models, prediction




```
> ml <- lm( weight ~ height, data=diet )
> nd <- data.frame( height = 150:190 )
> pr.co <- predict( ml, newdata=nd, interval="conf" )
> pr.pr <- predict( ml, newdata=nd, interval="pred" )
> with( diet, plot( weight ~ height, pch=16 )  )
> matlines( nd$height, pr.co, lty=1, lwd=c(5,2,2), col="blue" )
> matlines( nd$height, pr.pr, lty=2, lwd=c(5,2,2), col="blue" )
```

non-Linear models, prediction




```
> mq <- lm( weight ~ height + I(height^2), data=diet )
> pr.co <- predict( mq, newdata=nd, interval="conf" )
> pr.pr <- predict( mq, newdata=nd, interval="pred" )
> with( diet, plot( weight ~ height, pch=16 ) )
> matlines( nd$height, pr.co, lty=1, lwd=c(5,2,2), col="blue" )
> matlines( nd$height, pr.pr, lty=2, lwd=c(5,2,2), col="blue" )
```


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 0 ...
 $ Y: num  39650 36943 34588 33267 32614 ...

> head( testisDK )

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


Cases, PY and rates

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

-------------------------------------------------------------------------
          ---------------------------------P---------------------------------
A              1940      1950      1960      1970      1980      1990     Total
-------------------------------------------------------------------------
0             10.00      7.00     16.00     18.00      9.00     10.00     70.00
           2604.66   4037.31   3884.97   3820.88   3070.87   2165.54  19584.22
              0.38      0.17      0.41      0.47      0.29      0.46      0.36

10            13.00     27.00     37.00     72.00     97.00     75.00    321.00
           2135.73   3505.19   4004.13   3906.08   3847.40   2260.97  19659.48
              0.61      0.77      0.92      1.84      2.52      3.32      1.63

20           124.00    221.00    280.00    535.00    724.00    557.00   2441.00
           2225.55   2923.22   3401.65   4028.57   3941.18   2824.58  19344.74
              5.57      7.56      8.23     13.28     18.37     19.72     12.62
```

Linear effects in glm

How do rates depend on age?

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

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

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

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

Linear increase of log-rates by age

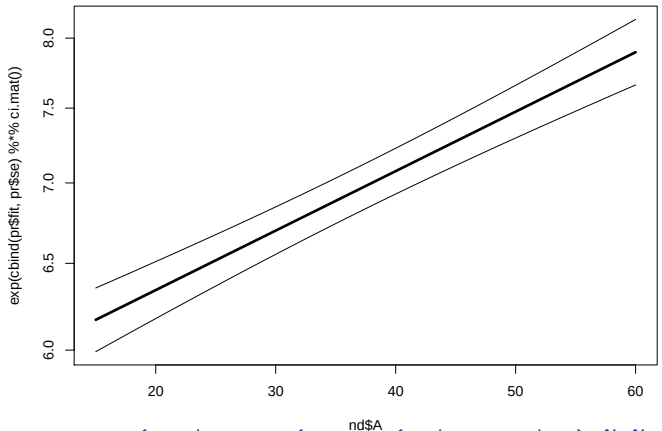
Linear effects in glm

```
> nd <- data.frame( A=15:60, Y=10^5 )
> pr <- predict( ml, newdata=nd, type="link", se.fit=TRUE )
> str( pr )

List of 3
 $ fit           : Named num [1:46] 1.82 1.83 1.83 1.84 1.84 ...
  ..- attr(*, "names")= chr [1:46] "1" "2" "3" "4" ...
 $ se.fit        : Named num [1:46] 0.015 0.0146 0.0143 0.014 0.0137 ...
  ..- attr(*, "names")= chr [1:46] "1" "2" "3" "4" ...
 $ residual.scale: num 1

> ci.mat()

     Estimate      2.5%    97.5%
[1,]        1  1.000000 1.000000
[2,]        0 -1.959964 1.959964

> matplot( nd$A, exp( cbind(pr$fit,pr$se) %*% ci.mat() ),
+          type="l", lty=1, lwd=c(3,1,1), col="black", log="y" )
```


Linear effects in glm

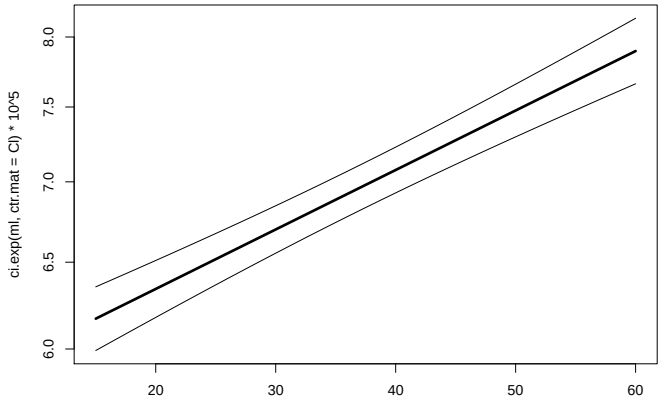
```
> round( ci.lin( ml ), 4 )

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

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

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

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

Linear effects in glm




```
> matplot( nd$A, exp( cbind(pr$fit,pr$se) %*% ci.mat() ),
+          type="l", lty=1, lwd=c(3,1,1), col="black", log="y" )
```


Linear effects in glm




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


Quadratic effects in glm

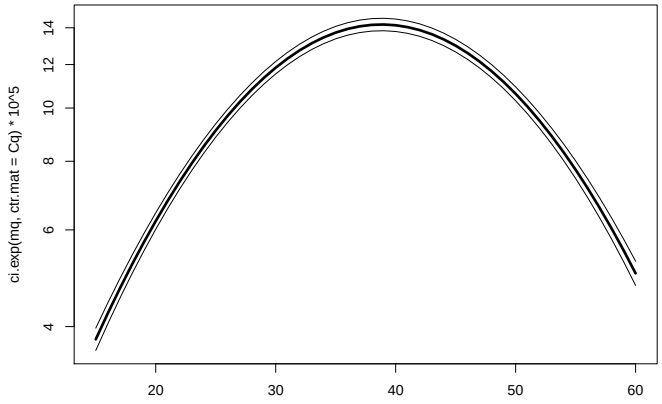
How do rates depend on age?

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

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

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

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

Quadratic effect in glm

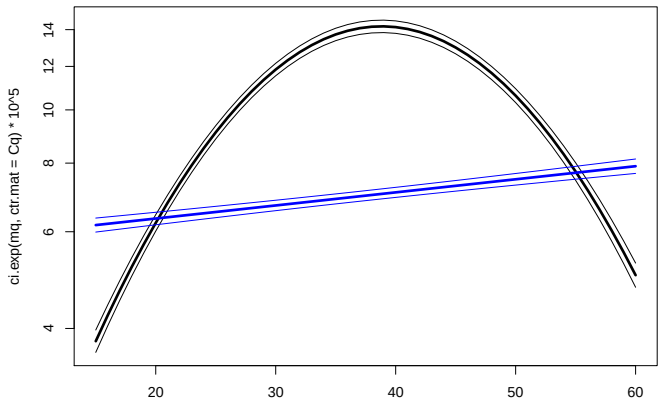
```
> round( ci.lin( mq ), 4 )

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

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

     [,1] [,2] [,3]
[1,]    1   15  225
[2,]    1   16  256
[3,]    1   17  289
[4,]    1   18  324
[5,]    1   19  361
[6,]    1   20  400

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


Quadratic effect in glm




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


Quadratic effect in glm




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

Spline effects in glm

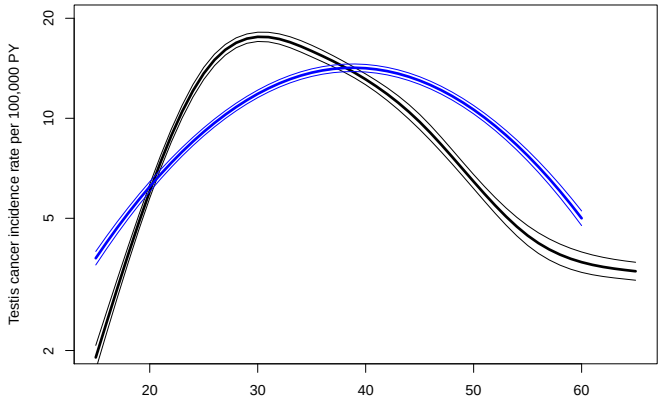
```
> library( splines )
> aa <- 15:65
> ms <- glm( D ~ Ns(A,knots=seq(15,65,10)),
+                offset=log(Y), family=poisson, data=testisDK )
> round( ci.exp( ms ), 3 )
```

```
                                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
```

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

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


Spline effects in glm




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


Adding a linear period effect

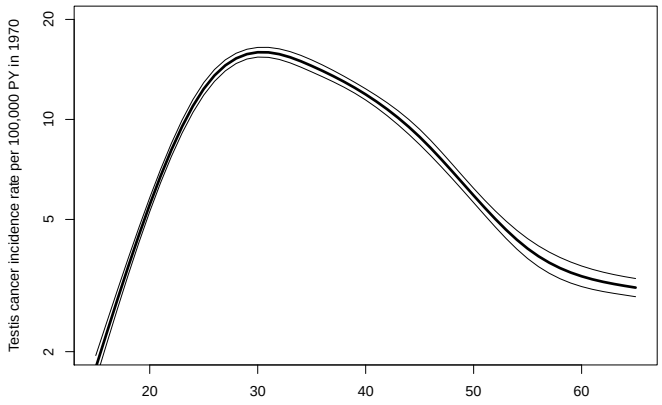
```
> msp <- glm( D ~ Ns(A,knots=seq(15,65,10)) + P,
+                 offset=log(Y), family=poisson, data=testisDK )
> round( ci.lin( msp ), 3 )
```

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

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

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

Adding a linear period effect




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


The period effect

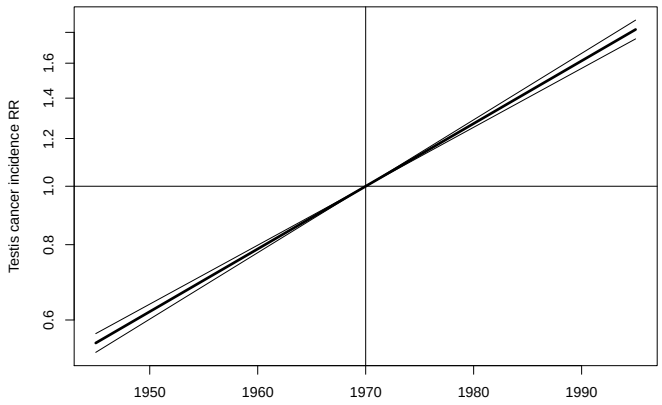
```
> round( ci.lin( msp ), 3 )
```

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

```
> pp <- 1945:1995
> Cp <- cbind( pp ) - 1970
> head( Cp )
```

```
      pp
[1,] -25
[2,] -24
[3,] -23
[4,] -22
[5,] -21
[6,] -20
```


Period effect

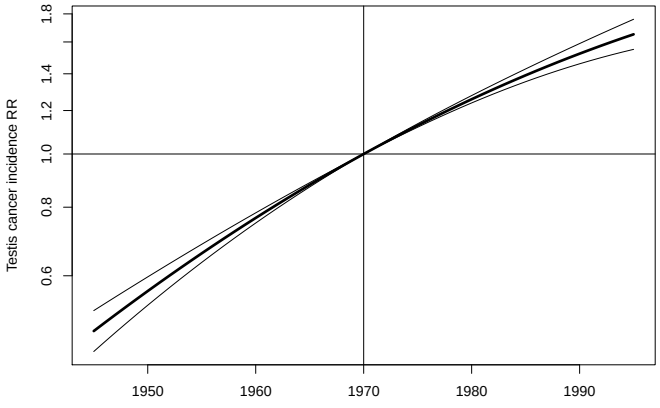



```
> matplot( pp, ci.exp( msp, subset="P", ctr.mat=Cp ),
+          log="y", xlab="Date", ylab="Testis cancer incidence RR",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
> abline( h=1, v=1970 )
```

A quadratic period effect

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

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

> pp <- 1945:1995
> Cq <- cbind( pp-1970, pp^2-1970^2 )
> head( Cq )

     [,1]   [,2]
[1,]  -25 -97875
[2,]  -24 -93984
[3,]  -23 -90051
```


A quadratic period effect




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

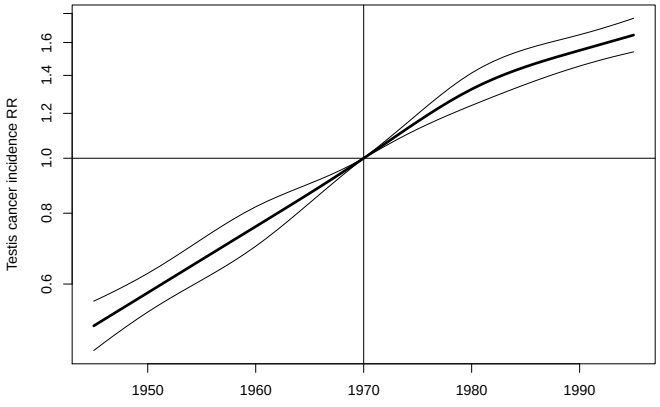

A spline period effect

```
> msps <- 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( msps ), 3 )

                                      exp(Est.)   2.5%  97.5%
(Intercept)                               0.000  0.000  0.000
Ns(A, knots = seq(15, 65, 10))1           8.327  7.452  9.305
Ns(A, knots = seq(15, 65, 10))2           5.528  4.842  6.312
Ns(A, knots = seq(15, 65, 10))3           1.007  0.894  1.133
Ns(A, knots = seq(15, 65, 10))4          13.447 11.107 16.279
Ns(A, knots = seq(15, 65, 10))5           0.458  0.422  0.497
Ns(P, knots = seq(1950, 1990, 10))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
```

A spline period effect

```
> pp <- 1945:1995
> Cs <- Ns(                pp  ,knots=seq(1950,1990,10))
> Cr <- Ns(rep(1970,length(pp)),knots=seq(1950,1990,10))
> head( Cs )

     1          2           3          4
[1,] 0 0.12677314 -0.38031941 0.25354628
[2,] 0 0.10141851 -0.30425553 0.20283702
[3,] 0 0.07606388 -0.22819165 0.15212777
[4,] 0 0.05070926 -0.15212777 0.10141851
[5,] 0 0.02535463 -0.07606388 0.05070926
[6,] 0 0.00000000  0.00000000 0.00000000

> head( Cr )

             1         2         3          4
[1,] 0.6666667 0.1125042 0.1624874 -0.1083249
[2,] 0.6666667 0.1125042 0.1624874 -0.1083249
[3,] 0.6666667 0.1125042 0.1624874 -0.1083249
[4,] 0.6666667 0.1125042 0.1624874 -0.1083249
[5,] 0.6666667 0.1125042 0.1624874 -0.1083249
[6,] 0.6666667 0.1125042 0.1624874 -0.1083249
```


Period effect

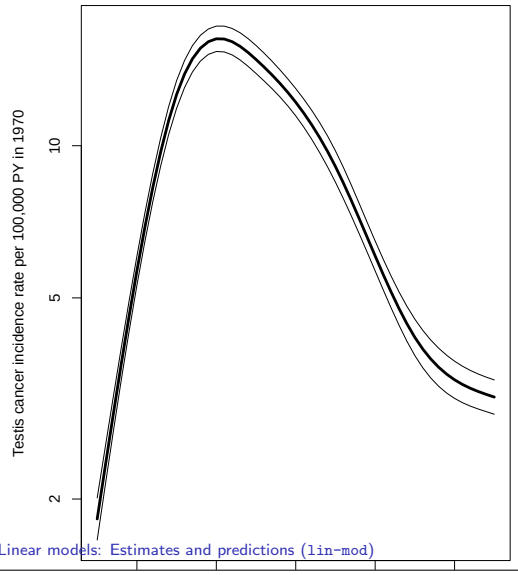


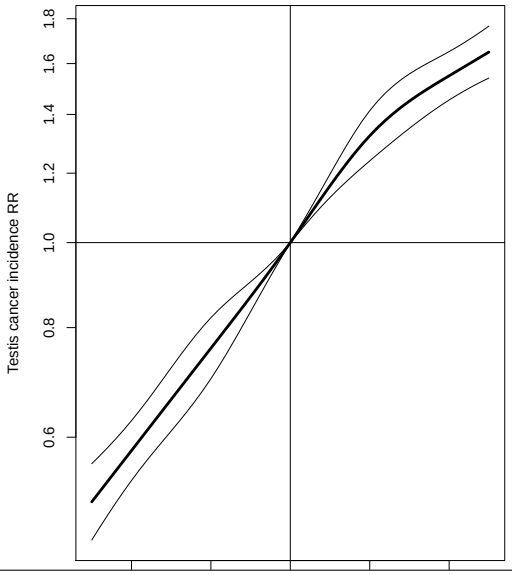

```
> matplot( pp, ci.exp( msps, subset="P", ctr.mat=Cs-Cr ),
+          log="y", xlab="Date", ylab="Testis cancer incidence RR",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
> abline( h=1, v=1970 )
```


Period effect

```
> par( mfrow=c(1,2) )
> Cap <- cbind( 1, Ns(                aa  ,knots=seq(15,65,10)),
+                  Ns(rep(1970,length(aa)),knots=seq(1950,1990,10)) )
> matplot( aa, ci.exp( msps, ctr.mat=Cap )*10^5,
+          log="y", xlab="Age",
+          ylab="Testis cancer incidence rate per 100,000 PY in 1970",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
> matplot( pp, ci.exp( msps, subset="P", ctr.mat=Cs-Cr ),
+          log="y", xlab="Date", ylab="Testis cancer incidence RR",
+          type="l", lty=1, lwd=c(3,1,1), col="black" )
> abline( h=1, v=1970 )
```

Age and period effect





Age and period effect with `ci.exp`

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

Recap of Monday — rates

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

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 scaling of t: $\Rightarrow$ smooth continuous effects of time
- . . . technically complicated:
- Construct `CA <- Ns(a.pt,knots=a.kn)`
- `ci.exp( model, ctr.mat=CA )`
- RR by period: `CP <- Ns(p.pt,knots=p.kn)`
  and: `CR <- Ns(rep(p.ref,nrow(CP)),knots=p.kn)`
- `ci.exp( model, ctr.mat=CP-CR)`
- . . . actually: `CP <- Ns(p.pt,knots=p.kn,ref=p.ref)`

Follow-up data

Statistical Analysis in the
Lexis Diagram:

Age-Period-Cohort models
May 2016
Max Planck Institut for Demographic Research, Rostock
http://BendixCarstensen/APC/MPIDR-2016

FU-rep-Lexis

Follow-up and rates

- Follow-up studies:
  - D — events, deaths
  - Y — person-years
  - $\lambda = D/Y$ rates
- Rates differ between persons.
- Rates differ within persons:
  - Along age
  - Along calendar time
- Multiple timescales.

Representation of follow-up data

In a cohort study we have records of:
Events and **Risk time**.

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

- Date of entry — date variable.
- Date of exit — date variable
- Status at exit — indicator-variable $(0/1)$

Specific for each *type* of outcome.

Aim of dividing time into bands:

Put $\begin{matrix} D & \text{— events} \\ Y & \text{— risk time} \end{matrix}$ in intervals on the timescale:

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?

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
```

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

Splitting the follow up

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

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

Splitting the follow-up

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

- but what if we want to keep track of calendar time too?

Timescales

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

Representation of follow-up on several timescales

- The time followed is the same on all timescales.
- Only use 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.

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

A follow-up study:

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

Timescales of interest:

- Age
- Calendar time
- Time since injection

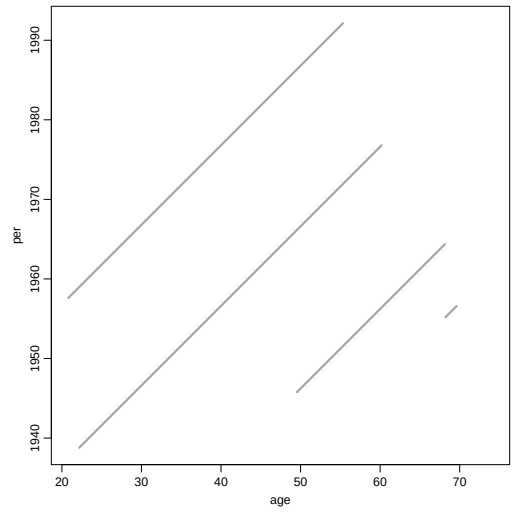
Definition of `Lexis` object

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

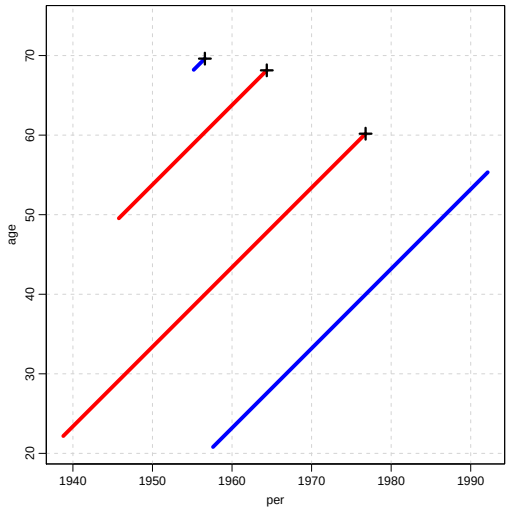
`entry` is defined on **three** timescales,
but `exit` is only defined on **one** timescale:
Follow-up time is the same on all timescales.

The looks of a `Lexis` object

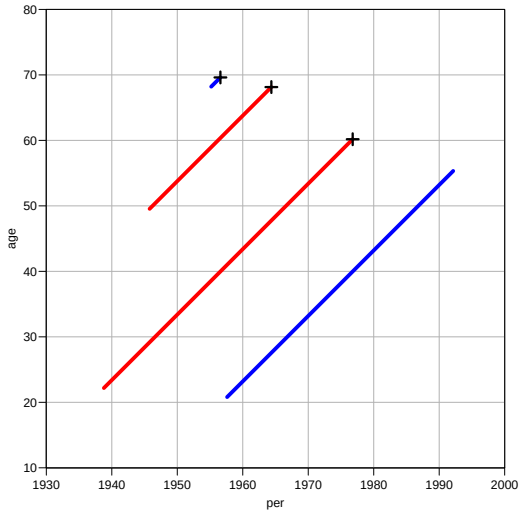
```
> round( thL[,c(1:8,14,15)], 2 )
    age     per tfi lex.dur lex.Cst lex.Xst lex.id   id exitdat exits
1 22.18 1938.79   0   38.00       0       1      1    1 1976.79
2 49.55 1945.77   0   18.60       0       1      2  640 1964.37
3 68.21 1955.18   0    1.40       0       1      3 3425 1956.59
4 20.80 1957.61   0   34.52       0       0      4 4017 1992.14
```


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




```
> plot( thL, 2:1, lwd=5, col=c("red","blue")[thL$contrast], grid=T )
> points( thL, 2:1, pch=c(NA,3)[thL$lex.Xst+1],lwd=3, cex=1.5 )
```


```
> 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 )
```


Splitting follow-up time

```
> spl1 <- splitLexis( thL, "age", breaks=seq(0,100,20) )
> round( spl1, 2 )
  lex.id   age     per   tfi lex.dur lex.Cst lex.Xst   id sex birthdat contrast
1      1 22.18 1938.79  0.00   17.82       0       0    1   2  1916.61        1
2      1 40.00 1956.61 17.82   20.00       0       0    1   2  1916.61        1
3      1 60.00 1976.61 37.82    0.18       0       1    1   2  1916.61        1
4      2 49.55 1945.77  0.00   10.45       0       0  640   2  1896.23        1
5      2 60.00 1956.23 10.45    8.14       0       1  640   2  1896.23        1
6      3 68.21 1955.18  0.00    1.40       0       1 3425   1  1886.97        2
7      4 20.80 1957.61  0.00   19.20       0       0 4017   2  1936.81        2
8      4 40.00 1976.81 19.20   15.33       0       0 4017   2  1936.81        2
```

Split on a second timescale

```
> # Split further on tfi:
> spl2 <- splitLexis( spl1, "tfi", breaks=c(0,1,5,20,100) )
> round( spl2, 2 )
   lex.id   age     per   tfi lex.dur lex.Cst lex.Xst   id sex birthdat
1       1 22.18 1938.79  0.00    1.00       0       0    1   2  1916.61
2       1 23.18 1939.79  1.00    4.00       0       0    1   2  1916.61
3       1 27.18 1943.79  5.00   12.82       0       0    1   2  1916.61
4       1 40.00 1956.61 17.82    2.18       0       0    1   2  1916.61
5       1 42.18 1958.79 20.00   17.82       0       0    1   2  1916.61
6       1 60.00 1976.61 37.82    0.18       0       1    1   2  1916.61
7       2 49.55 1945.77  0.00    1.00       0       0  640   2  1896.23
8       2 50.55 1946.77  1.00    4.00       0       0  640   2  1896.23
9       2 54.55 1950.77  5.00    5.45       0       0  640   2  1896.23
10      2 60.00 1956.23 10.45    8.14       0       1  640   2  1896.23
11      3 68.21 1955.18  0.00    1.00       0       0 3425   1  1886.97
12      3 69.21 1956.18  1.00    0.40       0       1 3425   1  1886.97
13      4 20.80 1957.61  0.00    1.00       0       0 4017   2  1936.81
14      4 21.80 1958.61  1.00    4.00       0       0 4017   2  1936.81
```


The Poisson likelihood for time-split data

One record per person-**interval** (i, t):

$$D\log(\lambda) - \lambda Y = \sum_{i,t} \left(d_{it}\log(\lambda) - \lambda y_{it} \right)$$

Assuming that the death indicator ($d_i \in \{0, 1\}$) is Poisson, with $\log$-offset y_i will give the same result.

The model assume that rates are constant.

But the split data allows relaxing this to models that assume different rates for different (d_{it}, y_{it}).

Where are the (d_{it}, y_{it}) in the split data?

The Poisson likelihood for time-split data

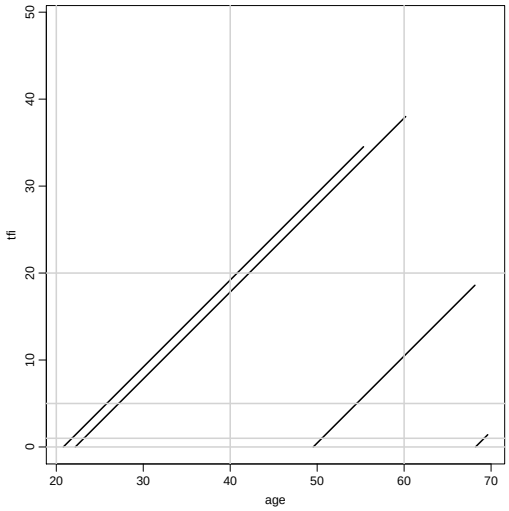
If $d \sim \text{Poisson}(\lambda y)$, i.e. with mean (λy) then the log-likelihood is

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

If we assume a multiplicative model for the rates, *i.e.* an additive model for the log-rates, we can use a Poisson model which is multiplicative in the mean, μ, i.e. linear in $\log(\mu)$:

$$\log(\mu) = \log(\lambda y) = \log(\lambda) + log(y)$$

Regression model must include $\log(y)$ as covariate with coefficient fixed to 1 — an offset-variable.




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


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

```
> round( spl2, 2 )
   lex.id   age     per   tfi lex.dur lex.Cst lex.Xst   id sex birthdat
1       1 22.18 1938.79  0.00    1.00       0       0    1   2  1916.61
2       1 23.18 1939.79  1.00    4.00       0       0    1   2  1916.61
3       1 27.18 1943.79  5.00   12.82       0       0    1   2  1916.61
4       1 40.00 1956.61 17.82    2.18       0       0    1   2  1916.61
5       1 42.18 1958.79 20.00   17.82       0       0    1   2  1916.61
6       1 60.00 1976.61 37.82    0.18       0       1    1   2  1916.61
7       2 49.55 1945.77  0.00    1.00       0       0  640   2  1896.23
8       2 50.55 1946.77  1.00    4.00       0       0  640   2  1896.23
9       2 54.55 1950.77  5.00    5.45       0       0  640   2  1896.23
10      2 60.00 1956.23 10.45    8.14       0       1  640   2  1896.23
11      3 68.21 1955.18  0.00    1.00       0       0 3425   1  1886.97
12      3 69.21 1956.18  1.00    0.40       0       1 3425   1  1886.97
13      4 20.80 1957.61  0.00    1.00       0       0 4017   2  1936.81
14      4 21.80 1958.61  1.00    4.00       0       0 4017   2  1936.81
15      4 25.80 1962.61  5.00   14.20       0       0 4017   2  1936.81
16      4 40.00 1976.81 19.20    0.80       0       0 4017   2  1936.81
```


Analysis of results

- d_i — events in the variable: `lex.Xst`.
- y_i — risk time: `lex.dur` (duration).
  Enters in the model via $\log(y)$ as offset.
- 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.

Poisson model for split data

- Each interval contribute λY to the log-likelihood.
- All intervals with the same set of covariate values (age,exposure,...) have the same λ.
- The log-likelihood contribution from these is $\lambda \sum Y$ — the same as from aggregated data.
- The event intervals contribute each $D\log\lambda$.
- The log-likelihood contribution from those with the same lambda is $\sum D\log\lambda$ — the same as from aggregated data.
- The log-likelihood is the same for split data and aggregated data — no need to tabulate first.

Models for tabulated data

Statistical Analysis in the
Lexis Diagram:

Age-Period-Cohort models
May 2016
Max Planck Institut for Demographic Research, Rostock
http://BendixCarstensen/APC/MPIDR-2016

tab-mod

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.

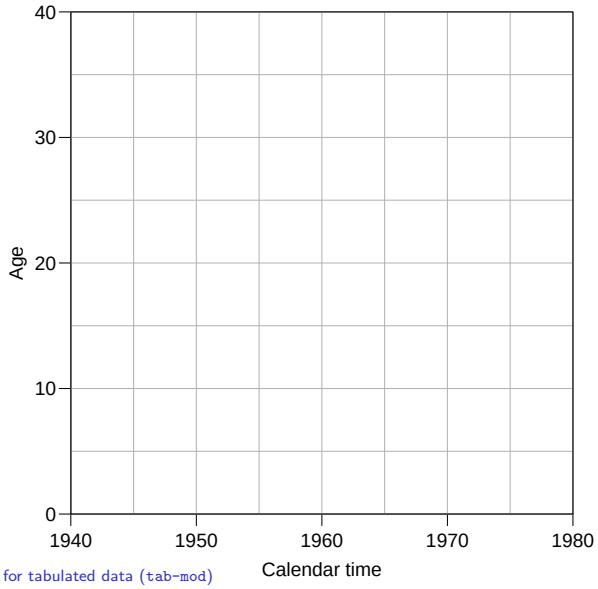
Realistic set-up

- 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.
  Or get it from the human mortality database.
- Analyse by Poisson model.

Lexis diagram [1]

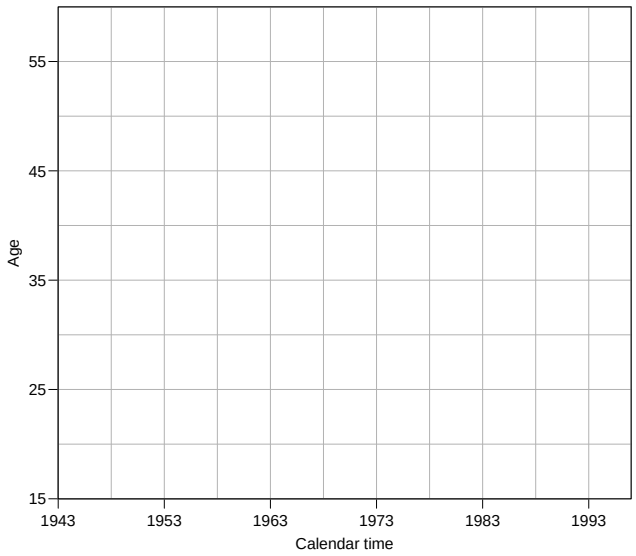


Disease registers record events.

Official statistics collect population data.

[1] Named after the German statistician and economist **William Lexis** (1837–1914), who devised this diagram in the book "Einleitung in die Theorie der Bevölkerungsstatistik" (Karl J. Trübner, Strassburg, 1875).

Lexis diagram



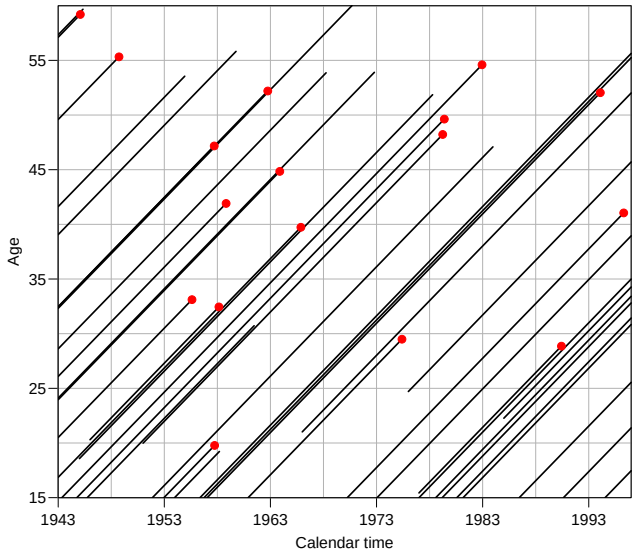
Registration of:

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.:

	Seminoma cases				Person-years			
Age	1943	1948	1953	1958	1943	1948	1953	1958
15	2	3	4	1	773812	744217	794123	972853
20	7	7	17	8	813022	744706	721810	770859
25	28	23	26	35	790501	781827	722968	698612
30	28	43	49	51	799293	774542	769298	711596
35	36	42	39	44	769356	782893	760213	760452
40	24	32	46	53	694073	754322	768471	749912

Reshape data to analysis form:

```
   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
1 15 1948  3 744217
2 20 1948  7 744706
3 25 1948 23 781827
4 30 1948 43 774542
5 35 1948 42 782893
6 40 1948 32 754322
1 15 1953  4 794123
2 20 1953 17 721810
3 25 1953 26 722968
4 30 1953 49 769298
5 35 1953 39 760213
6 40 1953 46 768471
1 15 1958  1 972853
```


Tabulated data

Once data are in tabular form, models are resticted:

- Rates must be assumed constant in each cell of the table / subset of the Lexis diagram.
- With large cells it is customary to put a separate paramter 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 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
```

`ci.lin()` from the `Epi` package extracts coefficients and computes confidence inetrvals:

```
> round( ci.lin( m0 ), 3 )
              Estimate StdErr      z     P   2.5%  97.5%
(Intercept)     -1.476  0.327 -4.517 0.000 -2.116 -0.836
factor(A)20      1.454  0.354  4.101 0.000  0.759  2.149
factor(A)25      2.532  0.330  7.671 0.000  1.885  3.179
factor(A)30      2.933  0.325  9.013 0.000  2.295  3.570
factor(A)35      2.861  0.326  8.779 0.000  2.223  3.500
factor(A)40      2.852  0.326  8.741 0.000  2.213  3.492
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
```


Subsets of parameter estimates accesed via a charcter string that is `grep`ed to the names.

```
> 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
```


Rates / rate-ratios are computed on the fly by `Exp=TRUE`:

```
> round( ci.lin( m0, subset="P", Exp=TRUE ), 3 )
              Estimate StdErr     z     P exp(Est.)  2.5% 97.5%
factor(P)1948    0.175  0.121 1.447 0.148     1.192 0.940 1.511
factor(P)1953    0.382  0.116 3.286 0.001     1.466 1.167 1.841
factor(P)1958    0.466  0.115 4.052 0.000     1.593 1.272 1.996
```

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

```
> CM <- rbind( c( 0,-1, 0),
+              c( 1,-1, 0),
+              c( 0, 0, 0),
+              c( 0,-1, 1) )
> round( ci.lin( m0, subset="P", ctr.mat=CM, Exp=TRUE ), 3 )
     Estimate StdErr      z     P exp(Est.)  2.5% 97.5%
[1,]   -0.382  0.116 -3.286 0.001     0.682 0.543 0.857
[2,]   -0.207  0.110 -1.874 0.061     0.813 0.655 1.010
[3,]    0.000  0.000    NaN   NaN     1.000 1.000 1.000
[4,]    0.084  0.104  0.808 0.419     1.087 0.887 1.332
```


Age-Period and Age-Cohort models

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Max Planck Institut for Demographic Research, Rostock
http://BendixCarstensen/APC/MPIDR-2016

AP-AC

Register data - rates

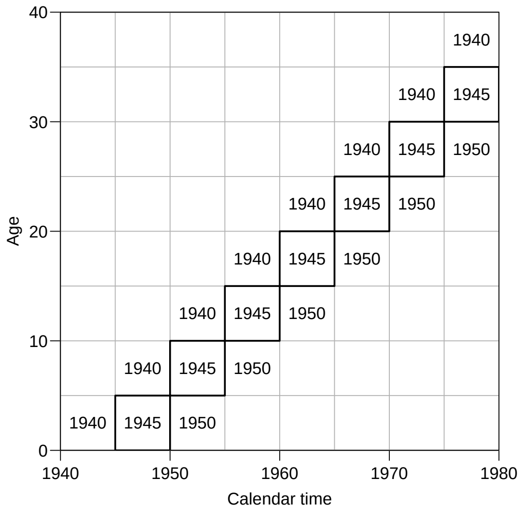
Rates in "tiles" of the Lexis diagram:

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

Descriptive epidemiology based on disease registers:
How do the rates vary across 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).

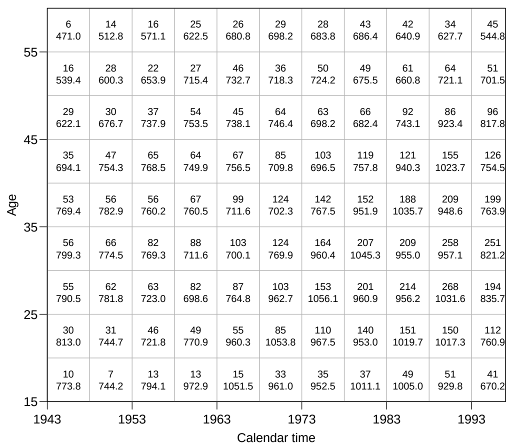
Synthetic cohorts



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

	Date of diagnosis $(year - 1900)$								
Age	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

Data matrix: Male risk time

1000 person-years

	Date of diagnosis $(year - 1900)$								
Age	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

Data matrix: Empirical rates

Rate per 1000,000 person-years

	Date of diagnosis $(year - 1900)$								
Age	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

The classical plots

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

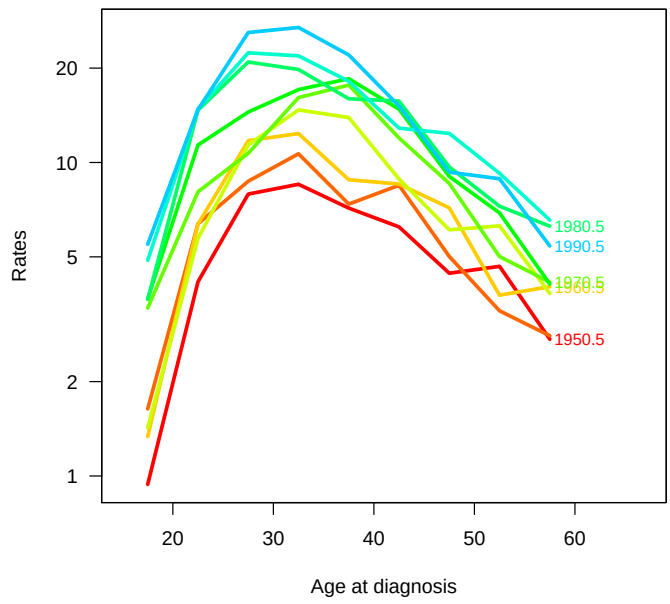
- Rates versus age at diagnosis (period):
  — rates in the same ageclass connected.
- Rates versus age at diagnosis:
  — rates in the same birth-cohort connected.
- Rates versus date of diagnosis:
  — rates in the same ageclass connected.
- Rates versus date of date of birth:
  — rates in the same ageclass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

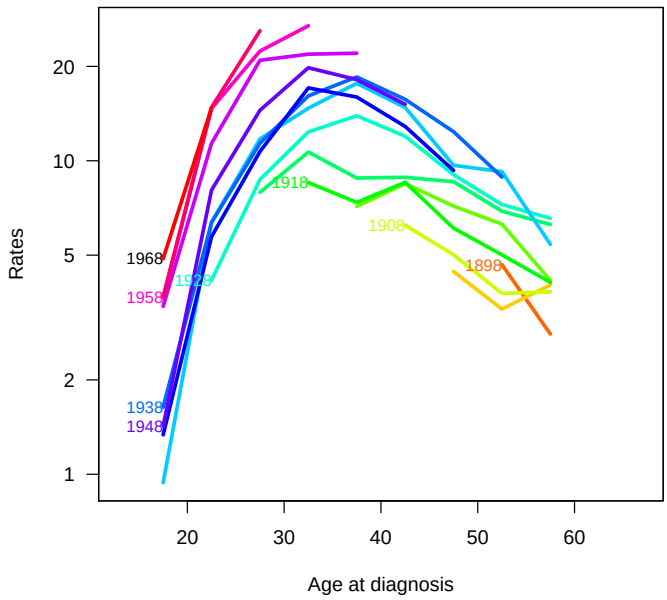
These plots can be produced by the R-function `rateplot`.

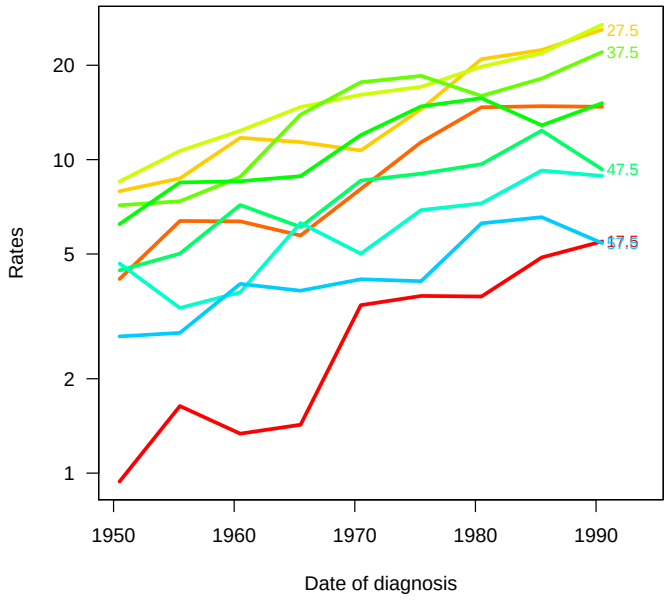
```
> library( Epi )
> load( file="../data/testisDK.Rda" )
> head( testisDK )

     A      P  D        Y
1 17.5 1950.5  7 744.2172
2 22.5 1950.5 31 744.7055
3 27.5 1950.5 62 781.8272
4 32.5 1950.5 66 774.5415
5 37.5 1950.5 56 782.8932
6 42.5 1950.5 47 754.3220

> xtabs( D ~ A + P, data = testisDK )

      P
A      1950.5 1955.5 1960.5 1965.5 1970.5 1975.5 1980.5 1985.5 1990.5
  17.5      7     13     13     15     33     35     37     49     51
  22.5     31     46     49     55     85    110    140    151    150
  27.5     62     63     82     87    103    153    201    214    268
  32.5     66     82     88    103    124    164    207    209    258
  37.5     56     56     67     99    124    142    152    188    209
  42.5     47     65     64     67     85    103    119    121    155
  47.5     30     37     54     45     64     63     66     92     86
  52.5     28     22     27     46     36     50     49     61     64
  57.5     14     16     25     26     29     28     43     42     34
```

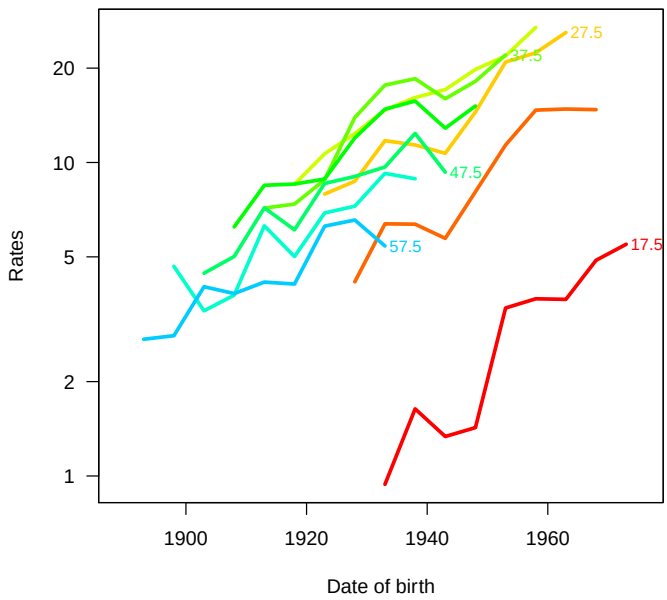


```
> wh = c("ap","ac","pa","ca")
> for( i in 1:4 ) {
+    pdf( paste("./graph/AP-AC-testisRate",i,".pdf",sep=""), height=6, width=6 )
+    par( mar=c(3,3,1,1, mgp=c(3,1,0)/1.6, bty="n", las=1 ))
+ rateplot( trate, wh[i], col=rainbow(15), lwd=3, ann=TRUE, a.lim=c(15,65) )
+    dev.off()
+    }
```


Rates
20
10
5
2
1
1968
1958
1938
1948
1918
1908
1898
20
30
40
50
60
Age at diagnosis


Rates
20
10
5
2
1
27.5
37.5
47.5
57.5
1950
1960
1970
1980
1990
Date of diagnosis


Rates
20
10
5
2
1
27.5
37.5
47.5
57.5
17.5
1900
1920
1940
1960
Date of birth

Age-period model

Rates are proportional between periods:

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

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

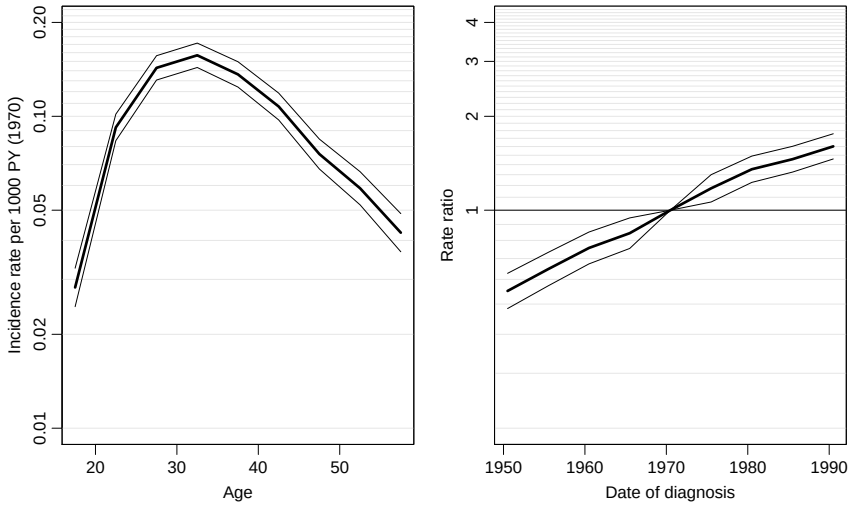
$$\log[\lambda(a,p_0)] = \alpha_a + \beta_{p_0} = \alpha_a$$

Fitting the model in R

Reference period is the 5th period (1970.5 $\sim$ 1968–72):

```
> ap <- glm( D ~ factor( A ) - 1 + relevel( factor( P ), 5 ) +
+                offset( log( Y ) ),
+            family=poisson )
> summary( ap )

Call:
glm(formula = D ~ factor(A) - 1 + relevel(factor(P), 5) + offset(log(Y)), family =

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-3.0925  -0.8784   0.1148   0.9790   2.7653

Coefficients:
                          Estimate Std. Error z value Pr(>|z|)
factor(A)17.5              -3.56605    0.07249 -49.194  < 2e-16
factor(A)22.5              -2.38447    0.04992 -47.766  < 2e-16
factor(A)27.5              -1.94496    0.04583 -42.442  < 2e-16
factor(A)32.5              -1.85214    0.04597 -40.294  < 2e-16
factor(A)37.5              -1.99308    0.04770 -41.787  < 2e-16
factor(A)42.5              -2.23017    0.05057 -44.104  < 2e-16
factor(A)47.5              -2.58125    0.05631 -45.839  < 2e-16
```


Graph of estimates with confidence intervals



Age-cohort model

Rates are proportional between cohorts:

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

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

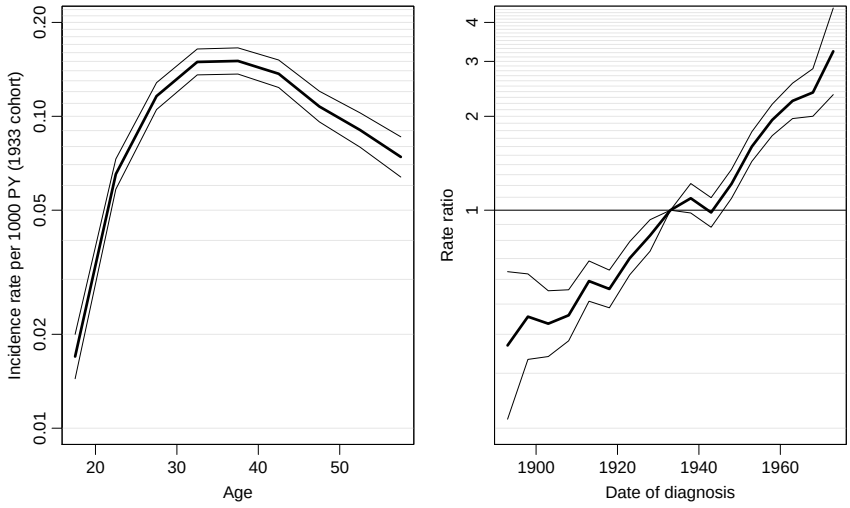
$$\log[\lambda(a, c_0)] = \alpha_a + \gamma_{c_0} = \alpha_a$$

Fit the model in R

Reference period is the 9th cohort (1933 $\sim$ 1928–38):

```
> ac <- glm( D ~ factor( A ) - 1 + relevel( factor( C ), 9 ) +
+                offset( log( Y ) ),
+                family=poisson )
> summary( ac )

Call:
glm(formula = D ~ factor(A) - 1 + relevel(factor(C), 9) + offset(log(Y)), family =

Deviance Residuals:
     Min        1Q    Median        3Q       Max
-1.92700  -0.72364  -0.02422   0.59623   1.87770

Coefficients:
                      Estimate Std. Error z value Pr(>|z|)
factor(A)17.5         -4.07597    0.08360 -48.753  < 2e-16
factor(A)22.5         -2.72942    0.05683 -48.031  < 2e-16
factor(A)27.5         -2.15347    0.05066 -42.505  < 2e-16
factor(A)32.5         -1.90118    0.04878 -38.976  < 2e-16
factor(A)37.5         -1.89404    0.04934 -38.387  < 2e-16
factor(A)42.5         -1.98846    0.05178 -38.399  < 2e-16
factor(A)47.5         -2.23047    0.05775 -38.626  < 2e-16
```


Graph of estimates with confidence intervals



Age-drift model

Statistical Analysis in the
Lexis Diagram:

Age-Period-Cohort models
May 2016
Max Planck Institut for Demographic Research, Rostock
http://BendixCarstensen/APC/MPIDR-2016

Ad

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

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 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
```


What goes on?

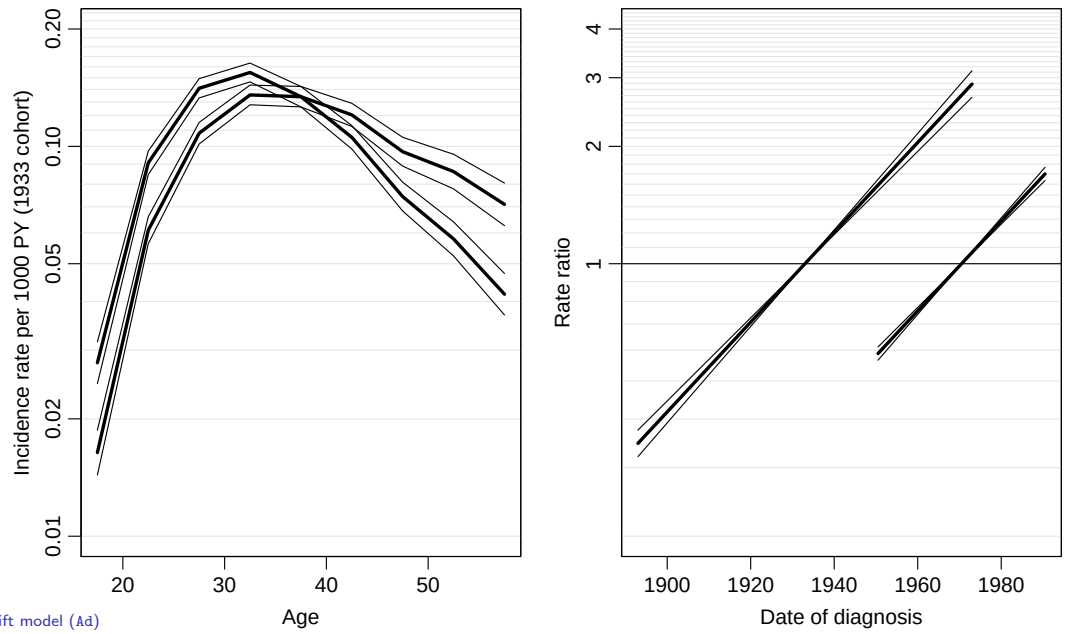
$$\alpha_a + \beta(p - p_0) = \alpha_a + \beta\big(a + c - (a_0 + c_0)\big)$$

$$= \underbrace{\alpha_a + \beta(a - a_0)}_{\text{cohort age-effect}} + \beta(c - c_0)$$

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).



Age at entry

Statistical Analysis in the
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Age-at-entry

Age at entry as covariate

t: time since entry
e: age at entry
$a = e + t$: current age

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

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

In a Cox-model with time since entry as time-scale, only the baseline hazard will change if age at entry is replaced by current age (a time-dependent variable).

Non-linear effects of time-scales

Arbitrary effects of the three variables t, a and e: $\Longrightarrow$ genuine extension of the model.

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

Three quantities can be arbitrarily moved between the three functions:

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

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 time.

Age-Period-Cohort model

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`APC-cat`

The age-period-cohort model

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

- Three effects:
  - Age (at diagnosis)
  - Period (of diagnosis)
  - Cohort (of birth)
- Modelled on the same *scale*.
- No assumptions about the *shape* of effects.
- Levels of `A`, `P` and `C` are assumed **exchangeable**
- no assumptions about the relationship of parameter estimates and the **scaled values** of `A`, `P` and `C`

Fitting the model in R I

```
> library( Epi )
> load( file="../data/testisDK.Rda" )
> head( testisDK )

     A      P  D        Y
1 17.5 1950.5  7 744.2172
2 22.5 1950.5 31 744.7055
3 27.5 1950.5 62 781.8272
4 32.5 1950.5 66 774.5415
5 37.5 1950.5 56 782.8932
6 42.5 1950.5 47 754.3220

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


Fitting the model in R II

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

Deviance Residuals:
     Min        1Q    Median        3Q       Max
-1.55709  -0.56174   0.01096   0.51221   1.32770

Coefficients: (1 not defined because of singularities)
                  Estimate Std. Error z value Pr(>|z|)
(Intercept)       -4.01129    0.16094 -24.925  < 2e-16
factor(A)22.5      1.23961    0.07745  16.005  < 2e-16
factor(A)27.5      1.70594    0.08049  21.194  < 2e-16
factor(A)32.5      1.83935    0.08946  20.561  < 2e-16
factor(A)37.5      1.71786    0.10217  16.813  < 2e-16
factor(A)42.5      1.48259    0.11708  12.663  < 2e-16
factor(A)47.5      1.09057    0.13447   8.110 5.07e-16
factor(A)52.5      0.76631    0.15271   5.018 5.22e-07
factor(A)57.5      0.41050    0.16094   2.551 0.010751
```


Fitting the model in R III

```
factor(P)1955.5    0.18645    0.07514   2.482 0.013082
factor(P)1960.5    0.37398    0.07949   4.705 2.54e-06
factor(P)1965.5    0.52062    0.08858   5.877 4.17e-09
factor(P)1970.5    0.72806    0.10013   7.271 3.56e-13
factor(P)1975.5    0.90736    0.11422   7.944 1.96e-15
factor(P)1980.5    1.02698    0.12978   7.913 2.51e-15
factor(P)1985.5    1.06237    0.14641   7.256 3.98e-13
factor(P)1990.5    1.10813    0.16094   6.885 5.76e-12
factor(P - A)1898  0.04216    0.29749   0.142 0.887290
factor(P - A)1903 -0.17670    0.26768  -0.660 0.509173
factor(P - A)1908 -0.27238    0.24294  -1.121 0.262210
factor(P - A)1913 -0.18041    0.22226  -0.812 0.416942
factor(P - A)1918 -0.39714    0.20763  -1.913 0.055787
factor(P - A)1923 -0.32538    0.19267  -1.689 0.091249
factor(P - A)1928 -0.30696    0.18046  -1.701 0.088936
factor(P - A)1933 -0.26626    0.16917  -1.574 0.115521
factor(P - A)1938 -0.32937    0.16103  -2.045 0.040813
factor(P - A)1943 -0.57450    0.15417  -3.727 0.000194
factor(P - A)1948 -0.49088    0.14858  -3.304 0.000954
```

Fitting the model in R IV

```
factor(P - A)1953 -0.32857    0.14601  -2.250 0.024430
factor(P - A)1958 -0.23140    0.14615  -1.583 0.113351
factor(P - A)1963 -0.18244    0.14978  -1.218 0.223200
factor(P - A)1968 -0.20961    0.16143  -1.298 0.194142
factor(P - A)1973       NA         NA      NA       NA

(Dispersion parameter for poisson family taken to be 1)

    Null deviance: 2463.197  on 80  degrees of freedom
Residual deviance:   35.459  on 49  degrees of freedom
AIC: 584.5

Number of Fisher Scoring iterations: 4
```

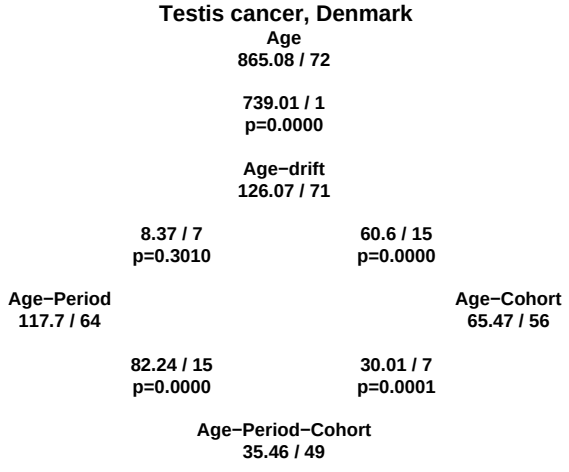

No. of parameters

A has 9 levels
P has 9 levels
$C = P - A$ has 17 levels

Age-drift model has $A + 1 = 10$ parameters
Age-period model has $A + P - 1 = 17$ parameters
Age-cohort model has $A + C - 1 = 25$ parameters
Age-period-cohort model has $A + P + C - 3 = 32$ parameters:

```
> length( coef(m.apc) )
[1] 33
> sum( !is.na(coef(m.apc)) )
[1] 32
```


Relationship of models



Test for effects

Model	Deviance	d.f.	p-value
Age - drift	126.07	71	
Δ	60.60	15	0.000
Age - cohort	65.47	56	
Δ	30.01	7	0.000
Age - period - cohort	35.46	49	
Δ	82.24	15	0.000
Age - period	117.70	64	
Δ	8.37	7	0.301
Age - drift	126.07	71	

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:

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

Putting it together again

Assumptions are needed, 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.

Period effect, on average 0, slope is 0:

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

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

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

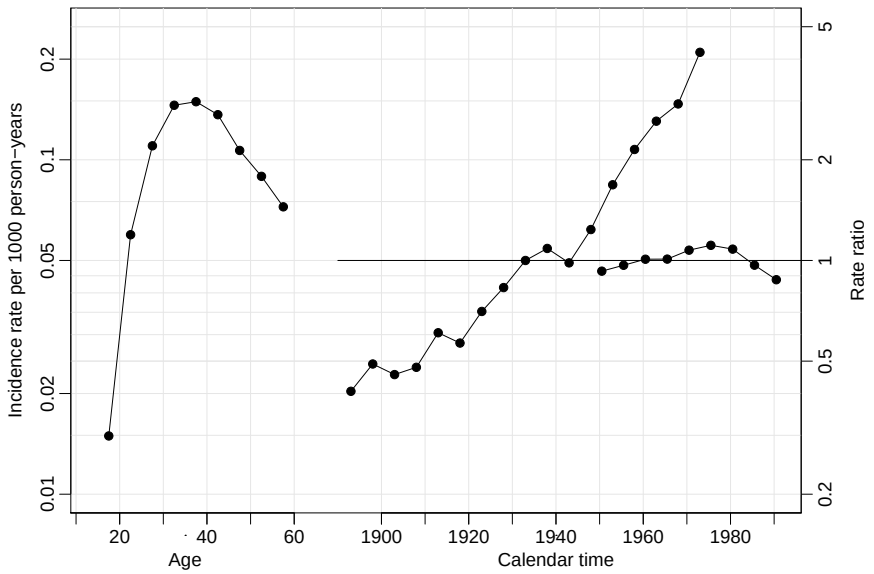
The rest is the age-effect:

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

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 $\hat{\gamma}_c$:

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

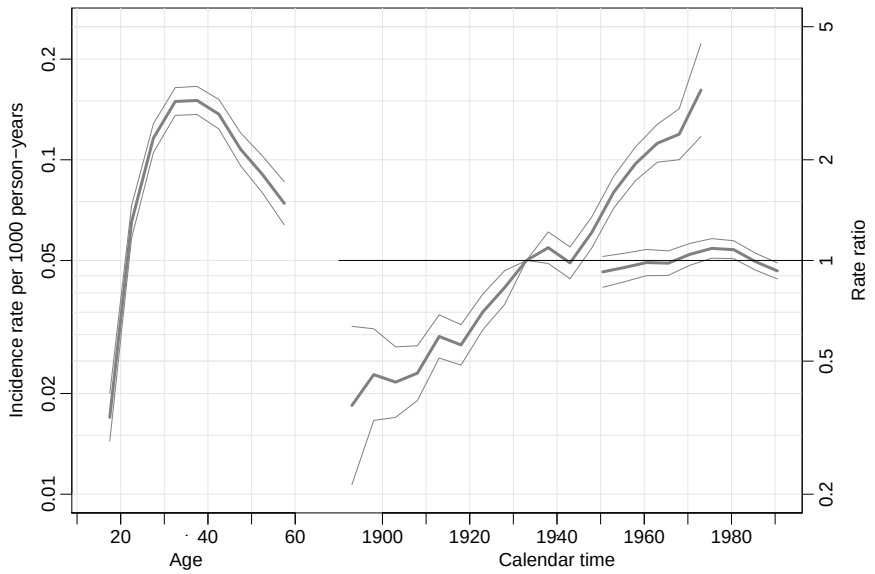
- Then consider the full APC-model with age and cohort effects as estimated:

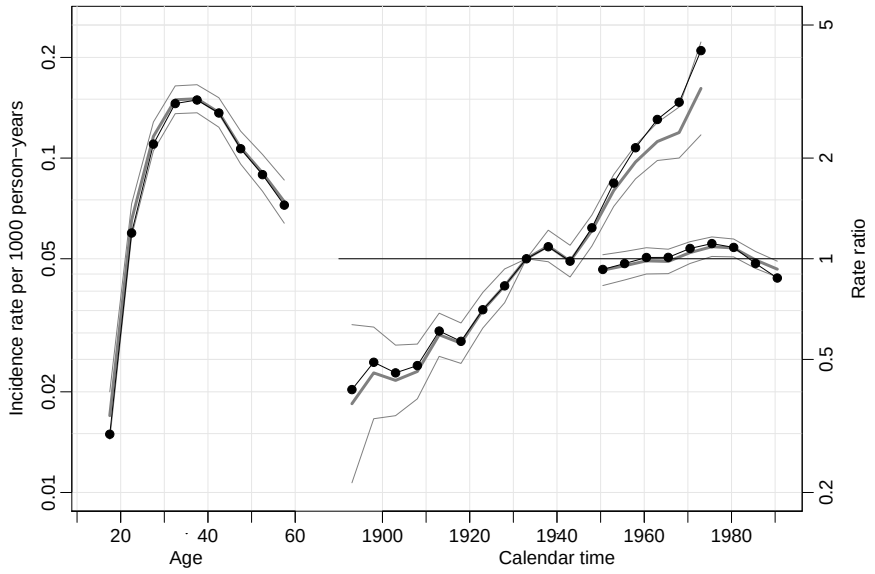
$$\log[\lambda(a,p)] = \hat{\alpha}_a + \hat{\gamma}_c + \beta_p$$

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

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

- 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.
- β_ps are estimated in a Poisson model with this as offset.
- Advantage: We get the standard errors for free.





Using contr.2nd I

```
> attach( testisDK )
> ( nA <- nlevels(factor(A)) )

[1] 9

> ( nP <- nlevels(factor(P)) )

[1] 9

> ( nC <- nlevels(factor(P-A)) )

[1] 17
```


Using contr.2nd II

```
> mp <- glm( D ~ factor(A) - 1 + I(P-1970) +
+             C( factor(P), contr.2nd, nP-2 ) +
+             C( factor(P-A), contr.2nd, nC-2 ),
+           offset = log(Y), family = poisson, data = testisDK )
> mc <- glm( D ~ factor(A) - 1 + I(P-A-1940) +
+             C( factor(P), contr.2nd, nP-2 ) +
+             C( factor(P-A), contr.2nd, nC-2 ),
+           offset = log(Y), family = poisson, data = testisDK )
> c( m.apc$deviance,
+    mp$deviance,
+    mc$deviance )

[1] 35.4587 35.4587 35.4587

> round( cbind( ci.exp(mp,subset="P)"),
+               ci.exp(mc,subset="P)") ), 4 )
```

Using contr.2nd III

```
                                exp(Est.)   2.5%  97.5% exp(Est.)   2.5%  97.5%
C(factor(P), contr.2nd, nP - 2)1    1.0011 0.7860 1.2751    1.0011 0.7860 1.2751
C(factor(P), contr.2nd, nP - 2)2    0.9599 0.7680 1.1998    0.9599 0.7680 1.1998
C(factor(P), contr.2nd, nP - 2)3    1.0627 0.8651 1.3053    1.0627 0.8651 1.3053
C(factor(P), contr.2nd, nP - 2)4    0.9722 0.8080 1.1699    0.9722 0.8080 1.1699
C(factor(P), contr.2nd, nP - 2)5    0.9421 0.7977 1.1126    0.9421 0.7977 1.1126
C(factor(P), contr.2nd, nP - 2)6    0.9192 0.7893 1.0706    0.9192 0.7893 1.0706
C(factor(P), contr.2nd, nP - 2)7    1.0104 0.8750 1.1668    1.0104 0.8750 1.1668

> round( rbind( ci.exp(mp,subset="I"),
+               ci.exp(mc,subset="I") ), 4 )

                exp(Est.)  2.5%  97.5%
I(P - 1970)        1.0468 0.926 1.1833
I(P - A - 1940)    1.0468 0.926 1.1833
```


Using contr.2nd IV

```
> matplot( sort(unique(testisDK$A)),
+          cbind(ci.exp(mp,subset="\\(A"),
+                ci.exp(mc,subset="\\(A"))*100,
+          log="y", xlab="Age", ylab="Incidence rate per 100,000 PY",
+          type="l",lty=1,lwd=c(3,1,1),col=rep(c("red","blue"),each=2) )
```


Tabulation in the Lexis diagram

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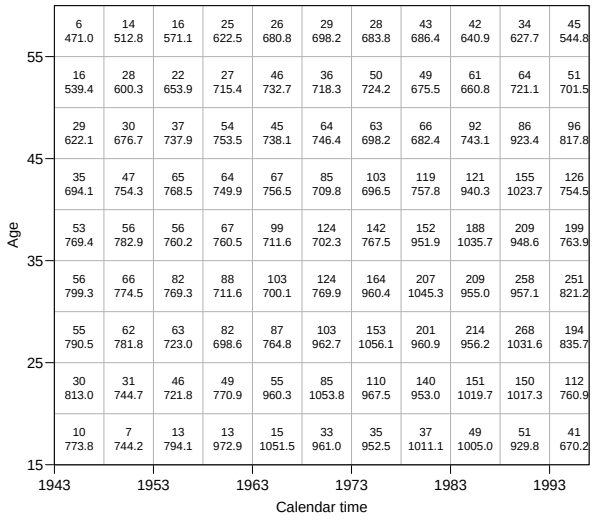
Lexis-tab

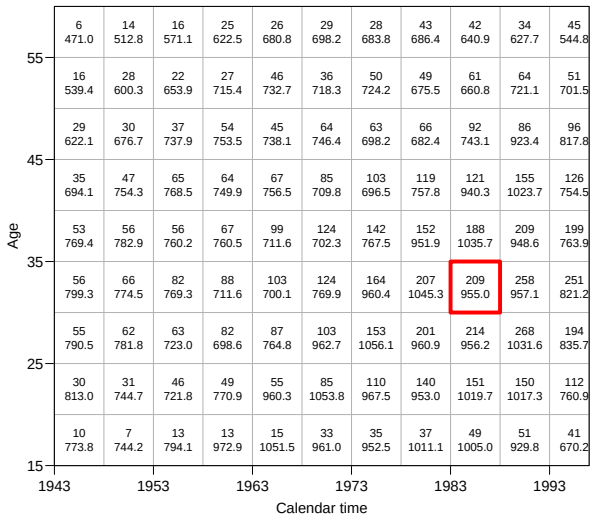
Tabulation of register data



Testis cancer cases in Denmark.

Male person-years in Denmark.

Tabulation of register data



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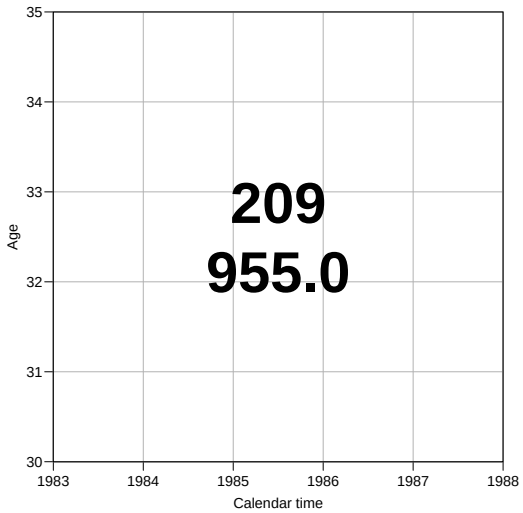

Testis cancer cases in Denmark.

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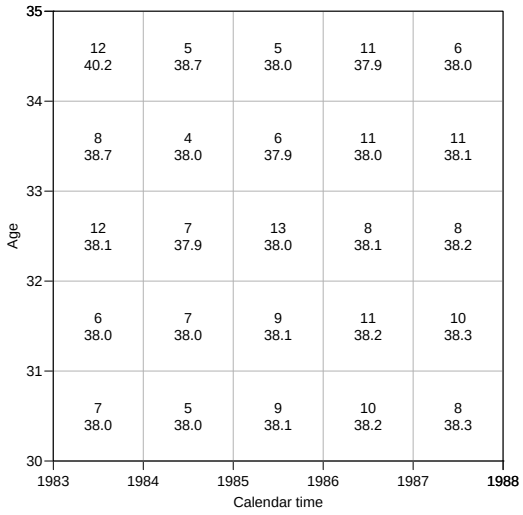
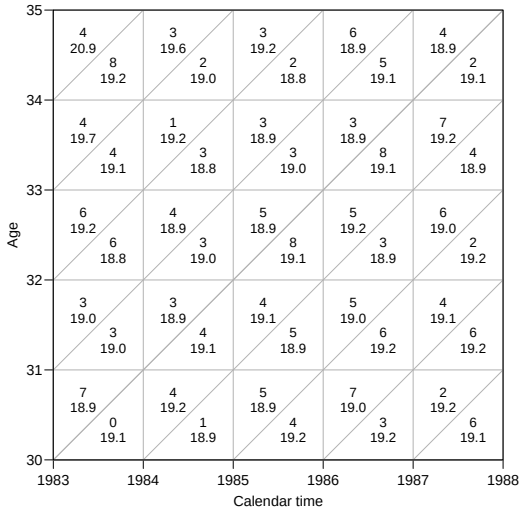
Tabulation of register data



Testis cancer cases in Denmark.

Male person-years in Denmark.

Tabulation of register data



Testis cancer cases in Denmark.

Male person-years in Denmark.

Subdivision by year of birth (cohort).

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 $a = p - c$.

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

We may classifiy cases and risk time by all three factors:

Upper triangles: Classification by age and period, earliest born cohort. ($\triangledown$)

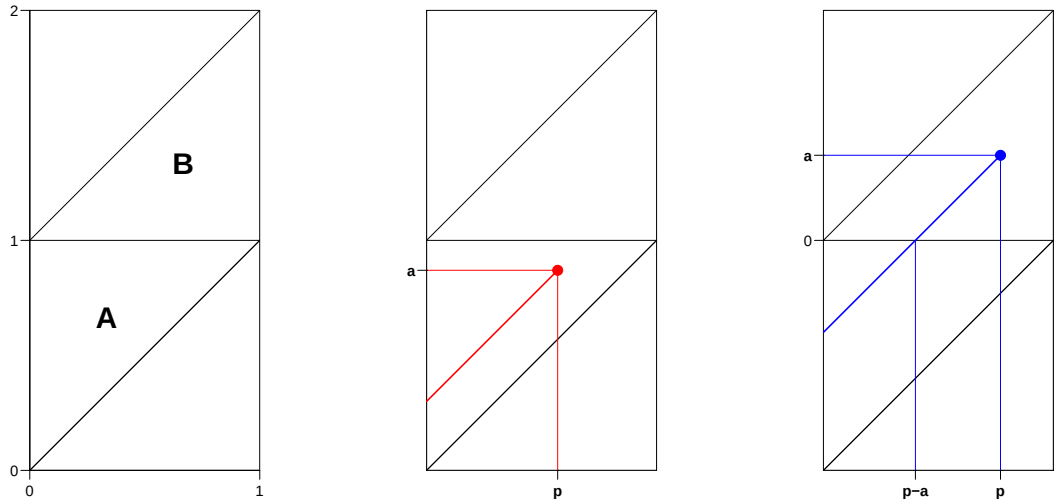
Lower triangles: Classification by age and cohort, last born cohort. ($\triangle$)

Mean time in triangles

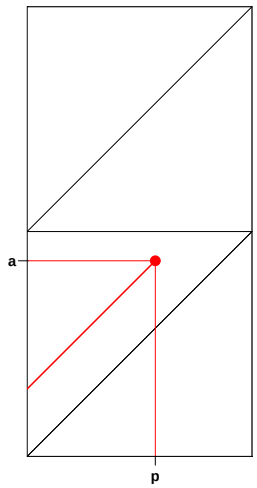
Modelling requires that each set (=observation in the dataset) be assigned a value of age, period and cohort. So for each triangle we need:

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

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



Upper triangles (◸), A:

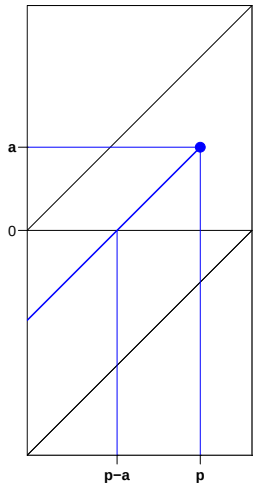


$$\mathrm{E}_{\mathbf{A}}(a) = \int_{p=0}^{p=1}\int_{a=p}^{a=1} a \times 2 \; \mathrm{d}a \; \mathrm{d}p = \int_{p=0}^{p=1} 1 - p^2 \; \mathrm{d}p = \frac{2}{3}$$

$$\mathrm{E}_{\mathbf{A}}(p) = \int_{a=0}^{a=1}\int_{p=0}^{p=a} p \times 2 \; \mathrm{d}p \; \mathrm{d}a = \int_{a=0}^{a=1} a^2 \; \mathrm{d}p = \frac{1}{3}$$

$$\mathrm{E}_{\mathbf{A}}(c) = \frac{1}{3} - \frac{2}{3} = -\frac{1}{3}$$

Lower triangles (◿), B:

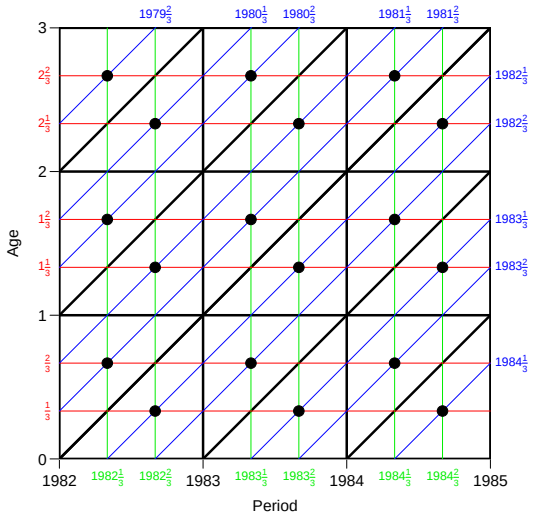


$$\mathrm{E}_{\mathbf{B}}(a) = \int_{p=0}^{p=1}\int_{a=0}^{a=p} a \times 2 \; \mathrm{d}a \; \mathrm{d}p = \int_{p=0}^{p=1} p^2 \; \mathrm{d}p = \frac{1}{3}$$

$$\mathrm{E}_{\mathbf{B}}(p) = \int_{a=0}^{a=1}\int_{p=a}^{p=1} p \times 2 \; \mathrm{d}p \; \mathrm{d}a = \int_{a=0}^{a=1} 1 - a^2 \; \mathrm{d}p = \frac{2}{3}$$

$$\mathrm{E}_{\mathbf{B}}(c) = \frac{2}{3} - \frac{1}{3} = \frac{1}{3}$$

Tabulation by age, period and cohort



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

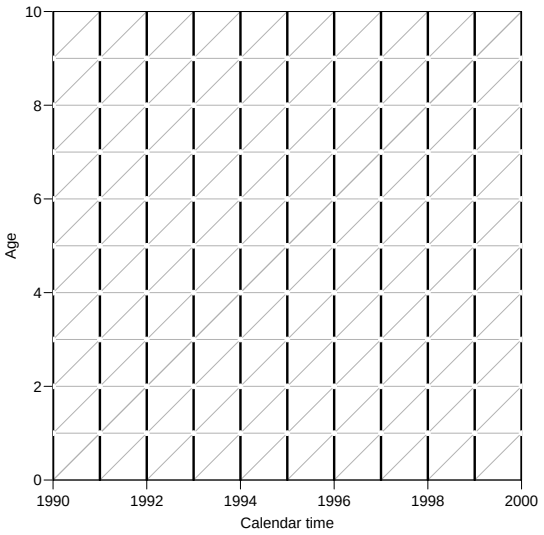
These correct midpoints for age, period and cohort must be used in modelling.

Population figures

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.

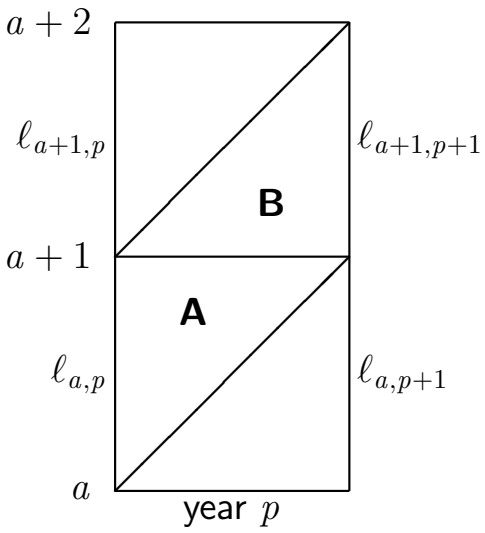
We want risk time figures for the population in the squares and triangles in the diagram.



Prevalent population figures

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

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

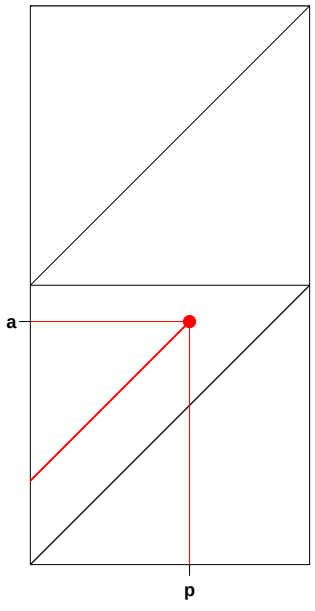


The area of the triangle is $1/2$, so the uniform measure over the triangle has density 2.
Therefore a person dying in age a at date p in **A** contributes p risk time, so the average will be:

$$\int_{p=0}^{p=1} \int_{a=p}^{a=1} 2p \; \mathrm{d}a \; \mathrm{d}p$$

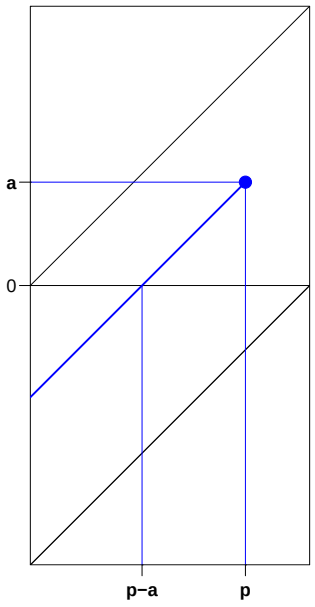
$$= \int_{p=0}^{p=1} 2p - 2p^2 \; \mathrm{d}p$$

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



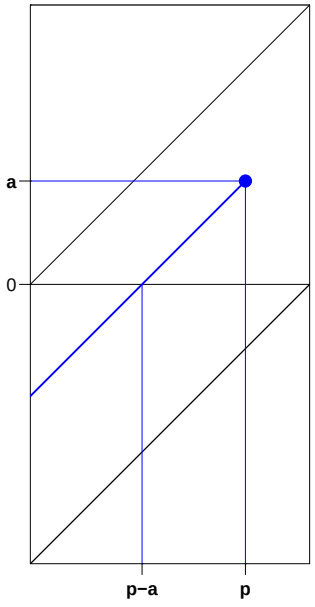
A person dying in age a at date p in **B** contributes $p - a$ risk time in **A**, so the average will be (agsing using the density 2 of the uniform measure):

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



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

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



Contributions to risk time in A and B:

	A:	**B**:
Survivors:	$\ell_{a+1,p+1} \times \frac{1}{2}$y	$\ell_{a+1,p+1} \times \frac{1}{2}$y
Dead in **A**:	$\frac{1}{2}(\ell_{a,p} - \ell_{a+1,p+1}) \times \frac{1}{3}$y	
Dead in **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
$\sum$	$(\frac{1}{3}\ell_{a,p} + \frac{1}{6}\ell_{a+1,p+1}) \times 1$y	$(\frac{1}{6}\ell_{a,p} + \frac{1}{3}\ell_{a+1,p+1}) \times 1$y

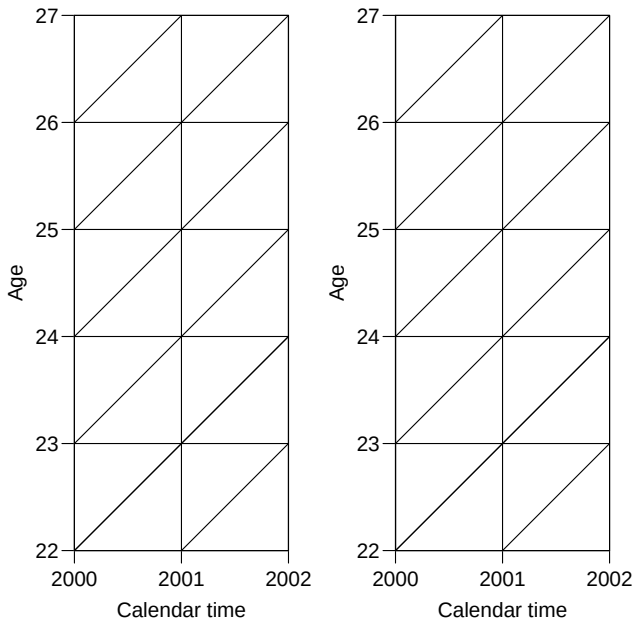
Population as of 1. January from Statistics Denmark:

	Men			Women		
	2000	2001	2002	2000	2001	2002
Age						
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

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 `Epi`.



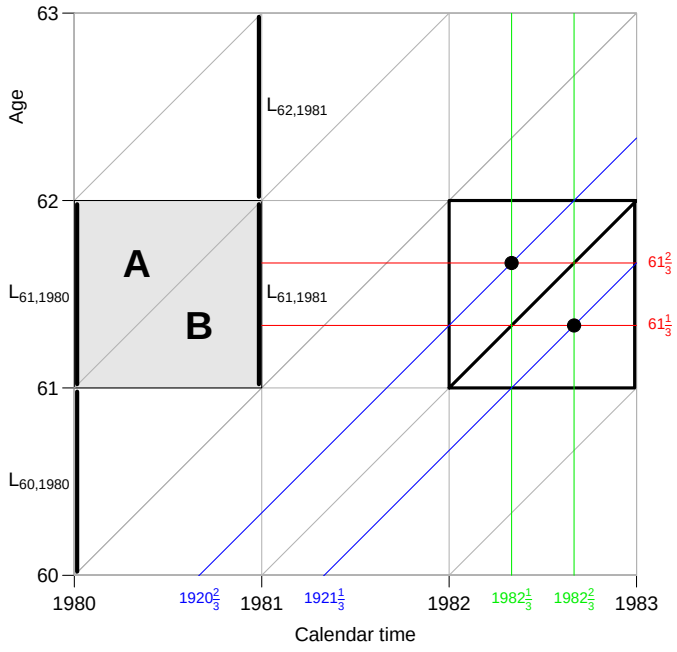
Summary:

Population risk time:

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

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

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



APC-model for triangular data

Statistical Analysis in the
Lexis Diagram:

Age-Period-Cohort models
May 2016
Max Planck Institut for Demographic Research, Rostock
http://BendixCarstensen/APC/MPIDR-2016

APC-tri

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:

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

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

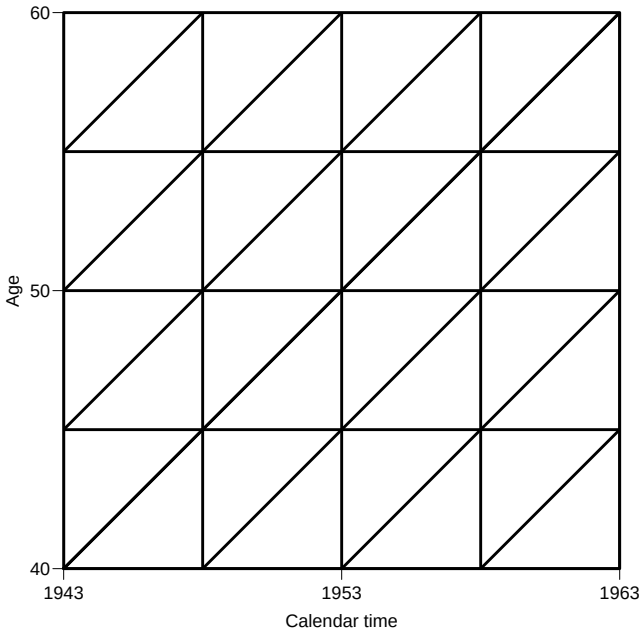
Illustration by lung cancer data

```
> 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
```


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.



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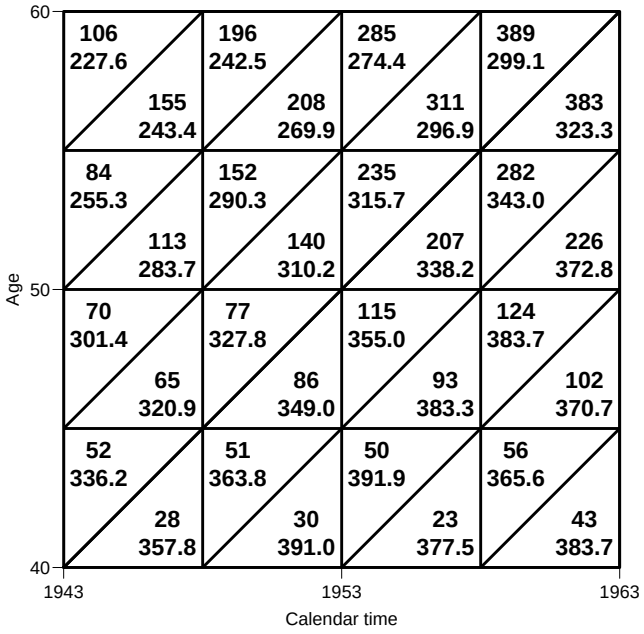


APC-model with “synthetic” cohorts

```
> 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: $220 - 182 = 38$.

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

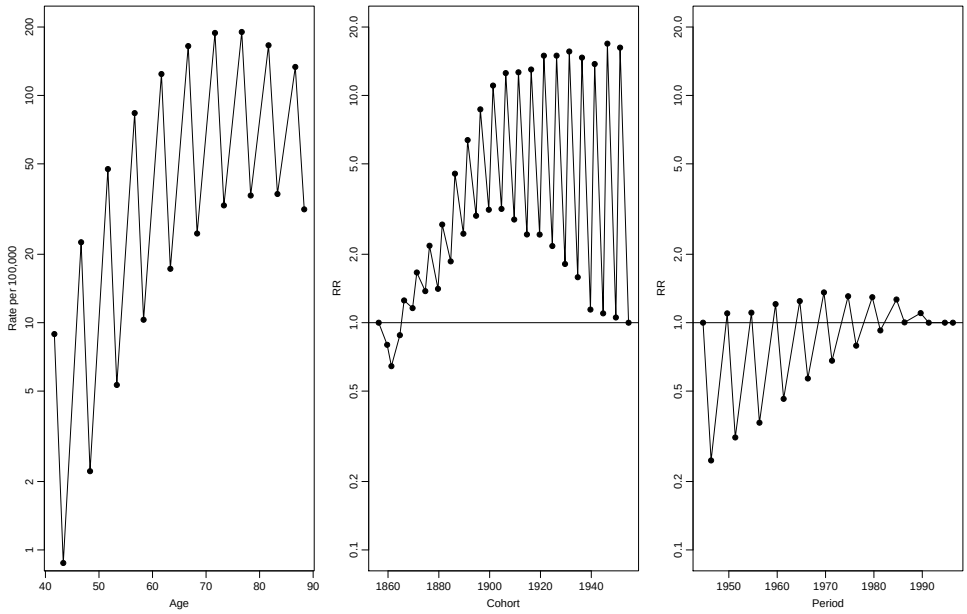
APC-model with “correct” cohorts

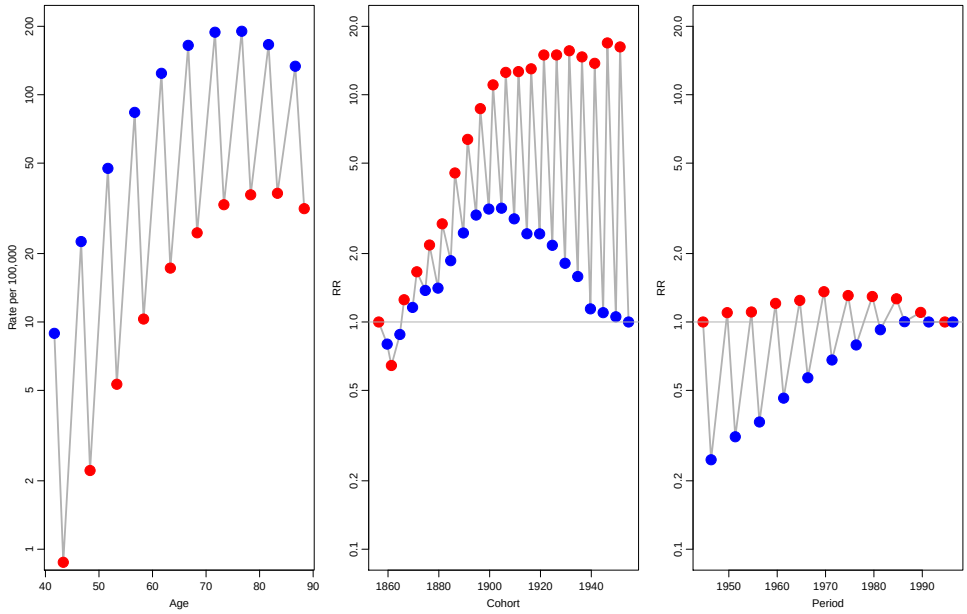
```
> mx <- glm( D ~ factor(Ax) - 1 +
+                factor(Cx) +
+                factor(Px) + offset( log( Y ) ),
+            family=poisson )
> summary( mx )
...
    Null deviance: 1.0037e+08  on 220  degrees of freedom
Residual deviance: 2.8473e+02  on 144  degrees of freedom
```

No. parameters: $220 - 144 = 76 \quad (= 38 \times 2)$.

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

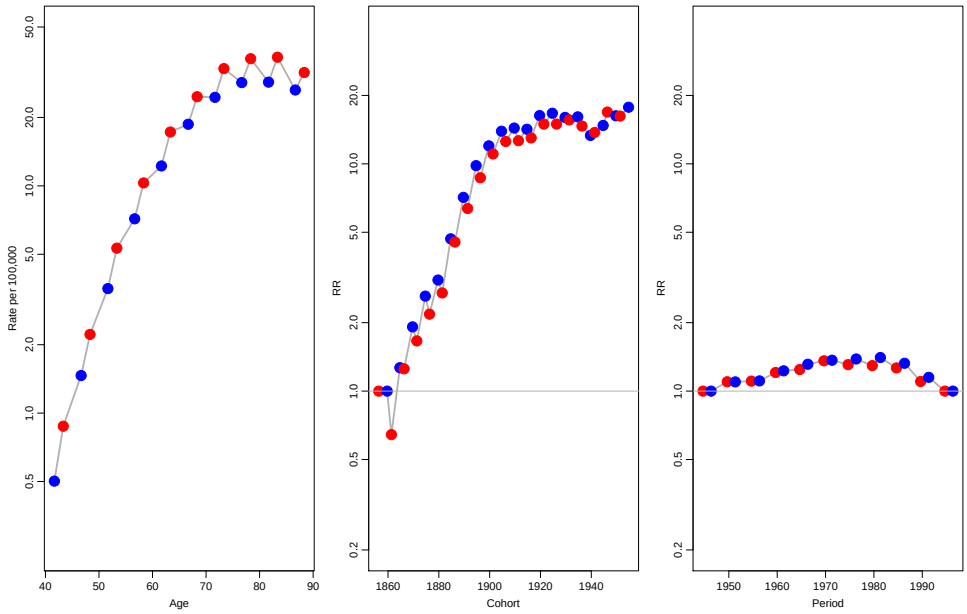
We have fitted two age-period-cohort models separately to upper and lower triangles.





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

APC-model: Parametrization

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`APC-par`

What's the problem?

- One parameter is assigned to each distinct value of the timescales, the **scale** of the variables ia 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.

The identifiability problem still exists:

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

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

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

Smooth functions

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

Possible choices for parametric functions describing the effect of the three continuous variables:

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

All of these contain the linear effect as special case.

Parametrization of effects

There are still three "free" parameters:

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

Any set of 3 numbers, μ_a, μ_c and γ will produce effects with teh same sum. Choose μ_a, μ_c and γ according to some criterion for the functions.

Parametrization principle

1. The age-function should be interpretable as log age-specific rates in 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).

Longitudinal or cohort age-effects.

Biologically interpretable — what happens during the lifespan of a cohort?

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.
- Cross-sectional or period age-effects?
- Bureaucratically interpretable — whats is seen at a particular date?

Might be wiser to look at predicted rates...

Implementation:

1. Obtain any set of parameters $f(a)$, $g(p)$, $h(c)$.
2. Extract the trend from the period effect (find μ and β):
$$\tilde{g}(p) = \hat{g}(p) - (\mu + \beta p)$$
3. Decide on a reference cohort c_0.
4. Use the functions:
$$\begin{aligned}\tilde{f}(a) &= \hat{f}(a) + \mu + \beta a + \hat{h}(c_0) + \beta c_0\\ \tilde{g}(p) &= \hat{g}(p) - \mu - \beta p\\ \tilde{h}(c) &= \hat{h}(c) \qquad + \beta c - \hat{h}(c_0) - \beta c_0\end{aligned}$$

These functions fulfill the criteria.

"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?
- How do we get the standard errors?
- Matrix-algebra!
- Projections!

Parametic function

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

Example: 2nd order polymomial:

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

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

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

Extract the trend from g:

- $$\langle \tilde{g}(p)|1\rangle = 0, \quad \langle \tilde{g}(p)|p\rangle = 0$$

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

Practical parametization

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 $\tilde{M}_{c_0}$.

4. Use:
   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 $\hat{\beta}_a$.

Information in the data and inner product

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

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

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

Log-lik for an observation (D, Y), with rate λ:

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

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

Information in the data and inner product

- Two inner products:

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

- Weights could be chosen as:
  - $w_i = D_i$, i.e. proportional to the information content for θ
  - $w_i = Y_i^2/D_i$, i.e. proportional to the information content for λ

How to? I

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

```
> library( Epi )
> sessionInfo()

R version 3.2.5 (2016-04-14)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Ubuntu 14.04.4 LTS

locale:
 [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C                LC_TIME=en_US.UTF-8
 [4] LC_COLLATE=en_US.UTF-8     LC_MONETARY=en_US.UTF-8     LC_MESSAGES=en_US.UTF-8
 [7] LC_PAPER=en_US.UTF-8       LC_NAME=C                   LC_ADDRESS=C
[10] LC_TELEPHONE=C             LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C

attached base packages:
[1] utils     datasets  graphics  grDevices stats     methods   base
```


How to? II

```
other attached packages:
[1] Epi_2.3

loaded via a namespace (and not attached):
 [1] cmprsk_2.2-7      MASS_7.3-44       Matrix_1.2-1      plyr_1.8.3        paral
 [6] survival_2.39-2   etm_0.6-2         Rcpp_0.11.6       splines_3.2.5     grid
[11] numDeriv_2014.2-1 lattice_0.20-31

> library( splines )
> data( lungDK )
> mw <- apc.fit( A=lungDK$Ax,
+                P=lungDK$Px,
+                D=lungDK$D,
+                Y=lungDK$Y/10^5, dr.extr="w", npar=8,
+            ref.c=1900 )
```

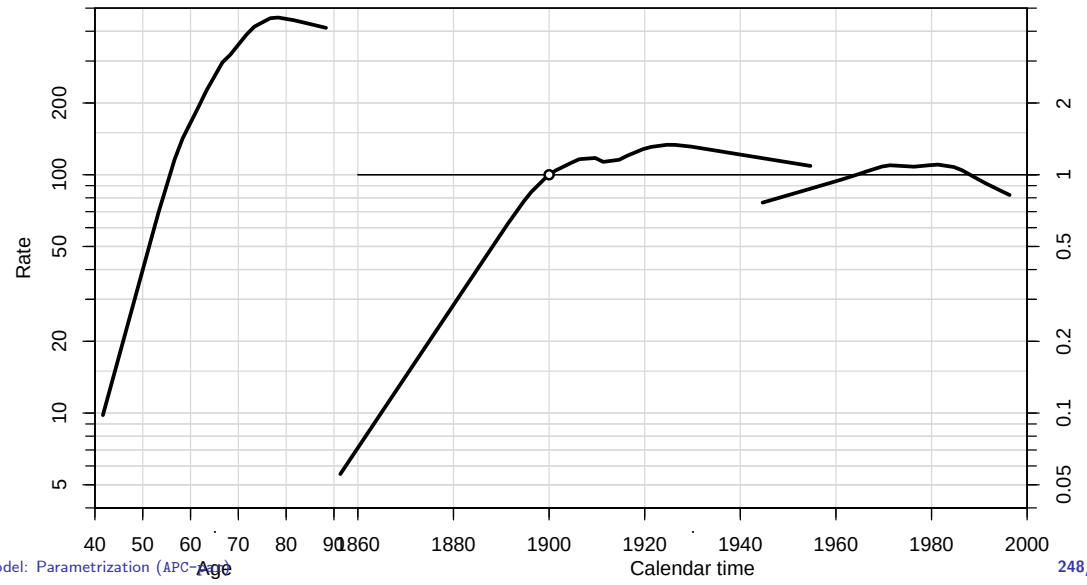

How to? III

```
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
```

How to? IV

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.



Other models I

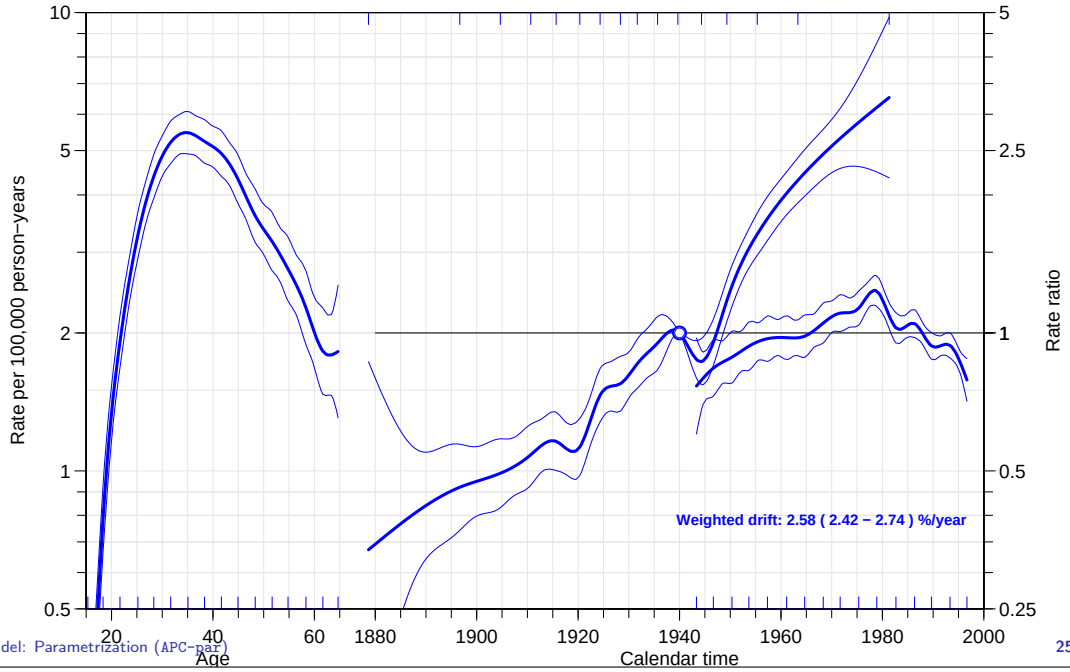
```
> ml <- apc.fit( A=lungDK$Ax,
+                P=lungDK$Px,
+                D=lungDK$D,
+                Y=lungDK$Y/10^5, dr.extr="1", npar=8,
+            ref.c=1900 )

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,
```

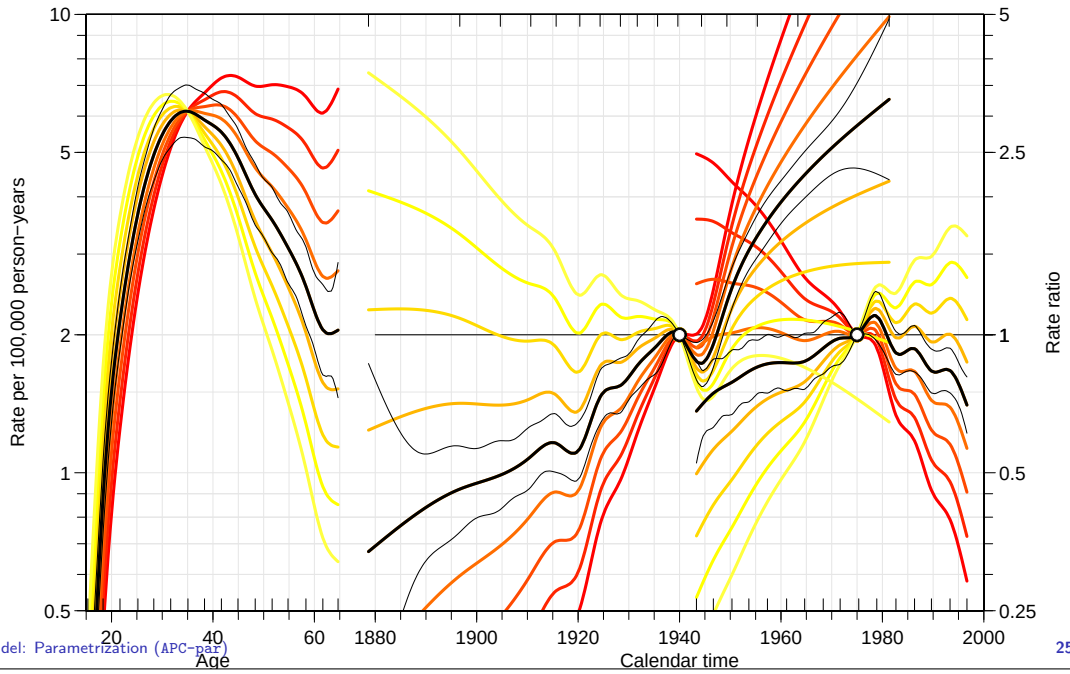


```
+                Y=lungDK$Y/10^5, dr.extr="1", npar=8,
+            ref.c=1900 )

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

> mw$Drift

                 exp(Est.)     2.5%    97.5%
APC (D-weights)  1.019662 1.019062 1.020263
A-d              1.023487 1.022971 1.024003

> ml$Drift
```



```
                   exp(Est.)     2.5%    97.5%
APC (Y2/D-weights)  1.014869 1.013687 1.016053
A-d                 1.023487 1.022971 1.024003

> m1$Drift

                 exp(Est.)     2.5%    97.5%
APC (1-weights)  1.033027 1.032174 1.033879
A-d              1.023487 1.022971 1.024003



> cnr <-
+ function( xf, yf )
+ {
+ cn <- par()$usr
+ xf <- ifelse( xf>1, xf/100, xf )
+ yf <- ifelse( yf>1, yf/100, yf )
+ xx <- ( 1 - xf ) * cn[1] + xf * cn[2]
+ yy <- ( 1 - yf ) * cn[3] + yf * cn[4]
+ if ( par()$xlog ) xx <- 10^xx
+ if ( par()$ylog ) yy <- 10^yy
+ list( x=xx, y=yy )
+ }
```


Rate per 100,000 person-years
Rate ratio
Age
Calendar time
Weighted drift: 2.58 (2.42 – 2.74) %/year


Rate per 100,000 person-years
Rate ratio
Age
Calendar time

Lee-Carter model

Statistical Analysis in the
Lexis Diagram:

Age-Period-Cohort models
May 2016
Max Planck Institut for Demographic Research, Rostock
`http://BendixCarstensen/APC/MPIDR-2016`

`LeeCarter`

Lee-Carter model for (mortality) rates

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

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.
- Relative **scaling** of b_x and k_t cannot be determined
- k_t only determined up to an **affine** transformation:

$$a_x + b_x(k_t + m) = (a_x + b_x m) = \tilde{a}_x + b_x k_t$$

Lee-Carter model in continuous time

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

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

$$f(a) + b(a)\big(k(t) + m\big) = (f(a) + b(a)m) = \tilde{f}(a) + b(a)k(t)$$

Lee-Carter model in continuous time

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

- 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×period interaction, but not a traditional one:

$$\log\big(\lambda(a,t)\big) = f(a) + b(a) \times k(t) = f(a) + k(t) + \big(b(a) - 1\big) \times k(t)$$

- Main effect and interaction component of t are constrained to be identical.
- **NOTE:** the time variable, t could be either period, p or cohort, $c = p - a$.

Main effect and interaction the same

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), ...
```


Main effect and interaction the same

Main effect and interaction component of t are constrained to,i=T be identical.

An interaction between two spline terms is **not** the same as the product of two terms:

```
> library( Epi )
> dfr <- data.frame( A=30:92, P=rep(1990:2010,3) )
> ( a.kn <- 4:8*10 ) ; ( p.kn <- c(1992+0:2*5) )

[1] 40 50 60 70 80

[1] 1992 1997 2002

> mA  <- with( dfr, model.matrix( ~ Ns(A,k=a.kn,i=T)              -1 ) )
> mP  <- with( dfr, model.matrix( ~                  Ns(P,k=p.kn)    ) )
> mAP <- with( dfr, model.matrix( ~ Ns(A,k=a.kn,i=T):Ns(P,k=p.kn) -1 ) )
> map <- with( dfr, model.matrix( ~ Ns(A,k=a.kn,i=T)*Ns(P,k=p.kn) -1 ) )
> cbind( colnames(mA) )
      [,1]
```

Lee-Carter model interpretation

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

- Constraints:
- $f(a)$ is the basic age-specific mortality
- $k(p)$ is the rate-ratio (RR) as a function of p:
  - relative to p_{ref} where $k(p_{\text{ref}}) = 1$
  - for persons aged a_{ref} where $b(a_{\text{ref}}) = 0$
- $b(a)$ is an age-specific multiplier for the RR
- Choose p_{ref} and a_{ref} *a priori*.

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 ages 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 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(*, "class")= chr [1:2] "xtabs" "table"
 - attr(*, "call")= language xtabs(formula = cbind(D, Y) ~ A + P, data = subset(lu
```

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" )
> str( lcM )
```


Lee-Carter with demography II

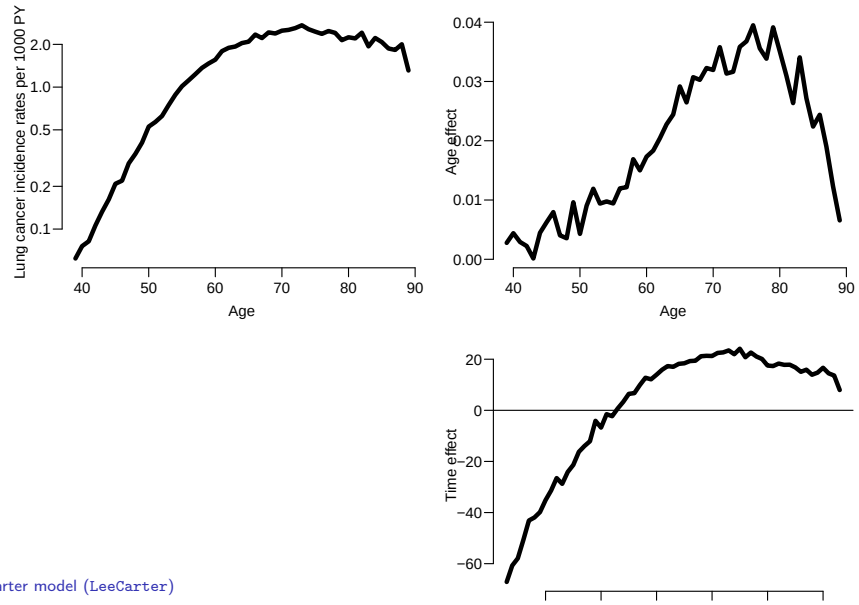
```
List of 7
 $ year  : num [1:61] 1943 1944 1945 1946 1947 ...
 $ age   : num [1:51] 39 40 41 42 43 44 45 46 47 48 ...
 $ rate  :List of 1
  ..$ Male: num [1:51, 1:61] 1.05e-04 7.10e-05 7.31e-05 3.73e-05 2.30e-04 ...
  .. ..- attr(*, "dimnames")=List of 2
  .. .. ..$ : chr [1:51] "39" "40" "41" "42" ...
  .. .. ..$ : chr [1:61] "1943" "1944" "1945" "1946" ...
 $ pop   :List of 1
  ..$ Male: num [1:51, 1:61] 28488 28152 27363 26791 26092 ...
  .. ..- attr(*, "dimnames")=List of 2
  .. .. ..$ : chr [1:51] "39" "40" "41" "42" ...
  .. .. ..$ : chr [1:61] "1943" "1944" "1945" "1946" ...
 $ type  : chr "Lung cancer incidence"
 $ label : chr "Denmark"
 $ lambda: num 1
 - attr(*, "class")= chr "demogdata"
```


Lee-Carter with demography III

`lca` estimation function checks the `type` argument, so we make a workaround:

```
> mrt <- function(x) { x$type <- "mortality" ; x }
> dmg.lcM <- lca( mrt(lcM), interpolate=TRUE )
> par( mfcol=c(2,2) )
> matplot( dmg.lcM$age, exp(dmg.lcM$ax)*1000,
+          log="y", ylab="Lung cancer incidence rates per 1000 PY",
+          xlab="Age", type="l", lty=1, lwd=4 )
> plot( NA, xlim=0:1, ylim=0:1, axes=FALSE, xlab="", ylab="" )
> matplot( dmg.lcM$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)
```

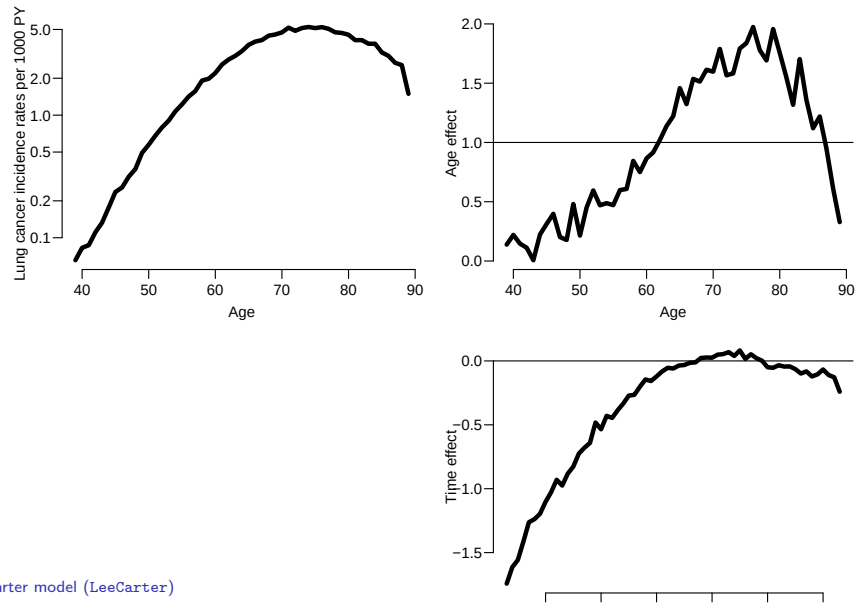
Lee-Carter with demography



Lee-Carter re-scaled I

```
> par( mfcol=c(2,2) )
> matplot( dmg.lcM$age, exp(dmg.lcM$ax+dmg.lcM$bx*20)*1000,
+          log="y", ylab="Lung cancer incidence rates per 1000 PY",
+          xlab="Age", type="l", lty=1, lwd=4 )
> plot( NA, xlim=0:1, ylim=0:1, axes=FALSE, xlab="", ylab="" )
> matplot( dmg.lcM$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 rescaled



Lee-Carter with `ilc`

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

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

- Age interaction with betewwn age and both period and/or cohort (=period-age)
- Extension of APC-model:
  $b(a) = 1$ and $a(a) = 1 \Leftrightarrow$ APC model.

Lee-Carter with `ilc` I

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

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 -
Note: 0 cells have 0/NA deaths and  0 have 0/NA exposure
  out of a total of 3111 data cells.
```


Lee-Carter with `ilc` II

```
 Starting values are:
    per per.c    age  age.c bx1.c
1  1943     0     39 -9.687  0.02
2  1944     0     40 -9.487  0.02
3  1945     0     41 -9.408  0.02
4  1946     0     42 -9.151  0.02
5  1947     0     43 -8.929  0.02
6  1948     0     44  -8.73  0.02
7  1949     0     45 -8.475  0.02
8  1950     0     46 -8.426  0.02
9  1951     0     47 -8.145  0.02
10 1952     0     48 -7.991  0.02
11 1953     0     49 -7.808  0.02
12 1954     0     50 -7.549  0.02
13 1955     0     51 -7.473  0.02
14 1956     0     52 -7.376  0.02
15 1957     0     53 -7.199  0.02
16 1958     0     54 -7.032  0.02
17 1959     0     55 -6.893  0.02
```

Lee-Carter with ilc III

```
18 1960     0     56 -6.798  0.02
19 1961     0     57 -6.698  0.02
20 1962     0     58 -6.596  0.02
21 1963     0     59 -6.524  0.02
22 1964     0     60 -6.463  0.02
23 1965     0     61 -6.325  0.02
24 1966     0     62 -6.271  0.02
25 1967     0     63  -6.25  0.02
26 1968     0     64 -6.194  0.02
27 1969     0     65 -6.171  0.02
28 1970     0     66 -6.056  0.02
29 1971     0     67 -6.113  0.02
30 1972     0     68 -6.021  0.02
31 1973     0     69 -6.039  0.02
32 1974     0     70 -5.993  0.02
33 1975     0     71  -5.98  0.02
34 1976     0     72 -5.951  0.02
35 1977     0     73 -5.905  0.02
36 1978     0     74 -5.969  0.02
```


Lee-Carter with ilc IV

```
37 1979     0     75 -6.008  0.02
38 1980     0     76 -6.044  0.02
39 1981     0     77 -5.998  0.02
40 1982     0     78 -6.029  0.02
41 1983     0     79 -6.146  0.02
42 1984     0     80   -6.1  0.02
43 1985     0     81 -6.118  0.02
44 1986     0     82 -6.025  0.02
45 1987     0     83 -6.247  0.02
46 1988     0     84 -6.111  0.02
47 1989     0     85 -6.177  0.02
48 1990     0     86 -6.281  0.02
49 1991     0     87 -6.305  0.02
50 1992     0     88 -6.213  0.02
51 1993     0     89 -6.638  0.02
52 1994     0
53 1995     0
54 1996     0
55 1997     0
```


Lee-Carter with ilc V

```
56 1998     0
57 1999     0
58 2000     0
59 2001     0
60 2002     0
61 2003     0

 Iterative fit:
 #iter   Dev    non-conv
    1  26123.55  0
     2  9403.337  0
     3  5219.715  0
     4  4269.859  0
     5  3982.804  0
     6  3878.544  0
     7  3836.703  0
     8  3818.834  0
     9  3810.839  0
     10  3807.133  0
```

Lee-Carter with ilc VI

```
        11  3805.368  0
        12  3804.512  0
        13  3804.089  0
        14  3803.878  0
        15  3803.772  0
        16  3803.718  0
        17  3803.69   0
        18  3803.676  0
        19  3803.669  0
        20  3803.665  0
        21  3803.663  0
        22  3803.662  0
        23  3803.661  0
        24  3803.661  0
        25  3803.661  0
        26  3803.661  0
        27  3803.66   0
        28  3803.66   0
        29  3803.66   0
```


Lee-Carter with ilc VII

```
        30  3803.66  0
        31  3803.66  0
        32  3803.66  0
        33  3803.66  0
        34  3803.66  0

    Iterations finished in: 34 steps

    Updated values are:
       per     per.c    age    age.c   bx1.c
1   1943 -67.11668     39 -9.54531  0.0019
2   1944 -64.24915     40 -9.34555 0.00613
3   1945 -59.06778     41 -9.27014 0.00171
4   1946 -54.10285     42 -9.03109 0.00174
5   1947 -47.71912     43 -8.79572 0.00036
6   1948 -44.96623     44 -8.64242 0.00348
7   1949 -39.87365     45  -8.4011 0.00422
8   1950 -36.46366     46 -8.35569 0.00618
9   1951 -38.65511     47 -8.08493 0.00431
```


Lee-Carter with ilc VIII

```
10 1952 -28.25000     48 -7.95317 0.00269
11 1953 -33.56753     49 -7.75764 0.00692
12 1954 -28.16299     50 -7.52418 0.00338
13 1955 -25.93964     51 -7.44269 0.00752
14 1956 -21.26733     52 -7.33407 0.01031
15 1957 -17.95370     53 -7.16891 0.00774
16 1958 -16.32569     54 -7.00417 0.00789
17 1959  -7.92142     55 -6.87498 0.00862
18 1960  -9.67085     56 -6.76735 0.01002
19 1961  -5.13527     57 -6.67977 0.01128
20 1962  -4.23977     58 -6.57225 0.01469
21 1963  -1.90709     59 -6.49916   0.013
22 1964  -0.65036     60  -6.4307  0.0152
23 1965   3.31265     61 -6.30139  0.0168
24 1966   4.51564     62   -6.247 0.01884
25 1967   7.16008     63 -6.20883 0.01935
26 1968  10.36382     64 -6.16206 0.02197
27 1969  10.60063     65 -6.11728 0.02439
28 1970  12.25461     66 -6.03717 0.02497
```

Lee-Carter with `ilc` IX

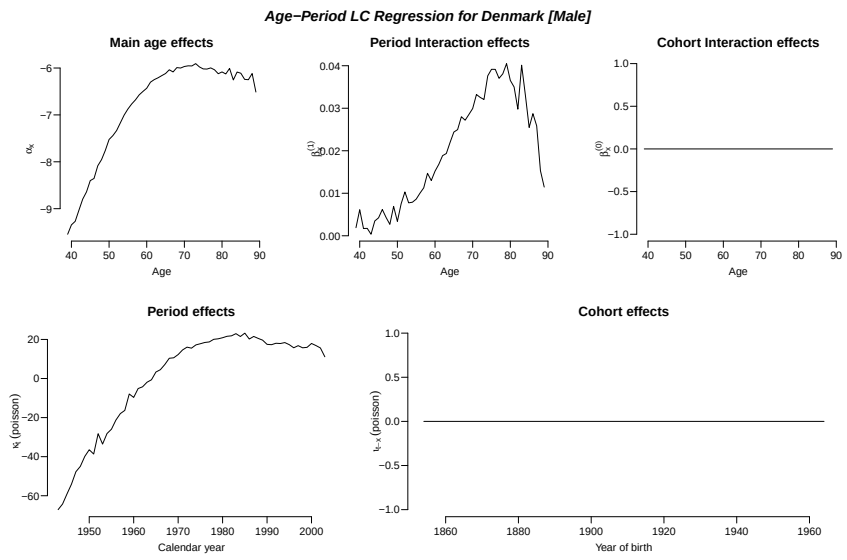
```
29 1971  14.63642     67 -6.08387   0.028
30 1972  16.05776     68 -5.99082 0.02718
31 1973  15.53593     69 -6.00028 0.02854
32 1974  17.21334     70 -5.96719 0.02994
33 1975  17.80268     71 -5.95329 0.03323
34 1976  18.44457     72  -5.9555 0.03255
35 1977  18.71973     73  -5.9058 0.03205
36 1978  20.06082     74 -5.97665 0.03762
37 1979  20.31816     75 -6.01915 0.03916
38 1980  20.87884     76 -6.02213 0.03915
39 1981  21.61232     77 -5.99743 0.03704
40 1982  21.85089     78 -6.03741 0.03809
41 1983  22.96473     79 -6.12152  0.0405
42 1984  21.50736     80 -6.08339 0.03654
43 1985  23.22937     81 -6.12649   0.035
44 1986  20.20563     82 -6.00846 0.02978
45 1987  21.53699     83  -6.2544 0.04013
46 1988  20.54046     84 -6.08511 0.03306
47 1989  19.63340     85 -6.11129 0.02548
```


Lee-Carter with `ilc` X

```
48 1990  17.48203     86 -6.24171 0.02873
49 1991  17.31414     87 -6.24948 0.02586
50 1992  18.04416     88 -6.11791 0.01529
51 1993  17.91747     89 -6.51232 0.01146
52 1994  18.39041
53 1995  17.32639
54 1996  15.72621
55 1997  16.81425
56 1998  15.71813
57 1999  15.95432
58 2000  17.93764
59 2001  16.86795
60 2002  15.63661
61 2003  11.11935
 total sums are:
 b0  b1 itx  kt
  0   1   0   0
```

```
> plot( ilc.lcM )
```


Lee-Carter with `ilc`



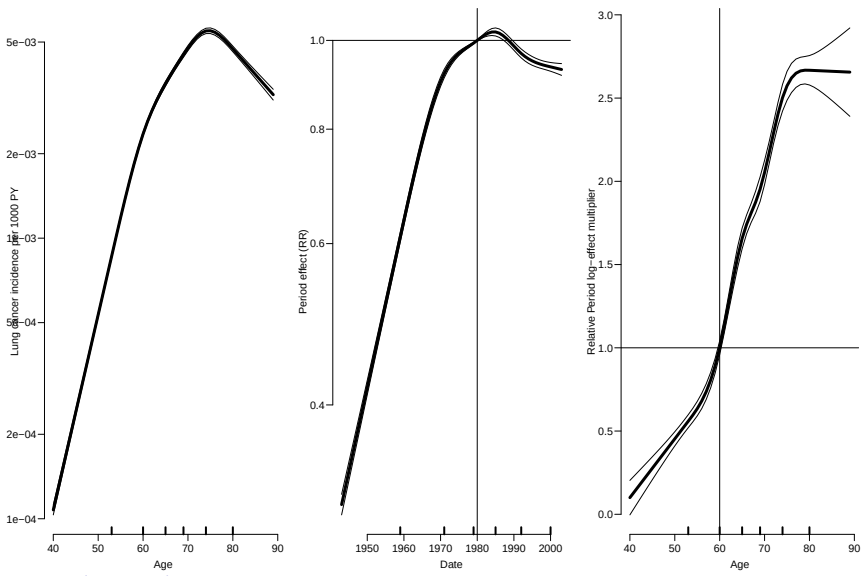
Lee-Carter with Epi

- `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 algoritm alternately fits a main age and period effects and the age-interaction effect.

Lee-Carter with Epi I

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

LCa.fit convergence in  11  iterations, deviance: 8566.554 on 6084 d.f.

> LCa.Mlc

Lee-Carter model using natural splines:
  log(Rate) = a(Age) + b(Age)k(Period)
with 6, 5 and 6 parameters respectively (1 aliased).
Deviance: 8566.554 on 6084 d.f.

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

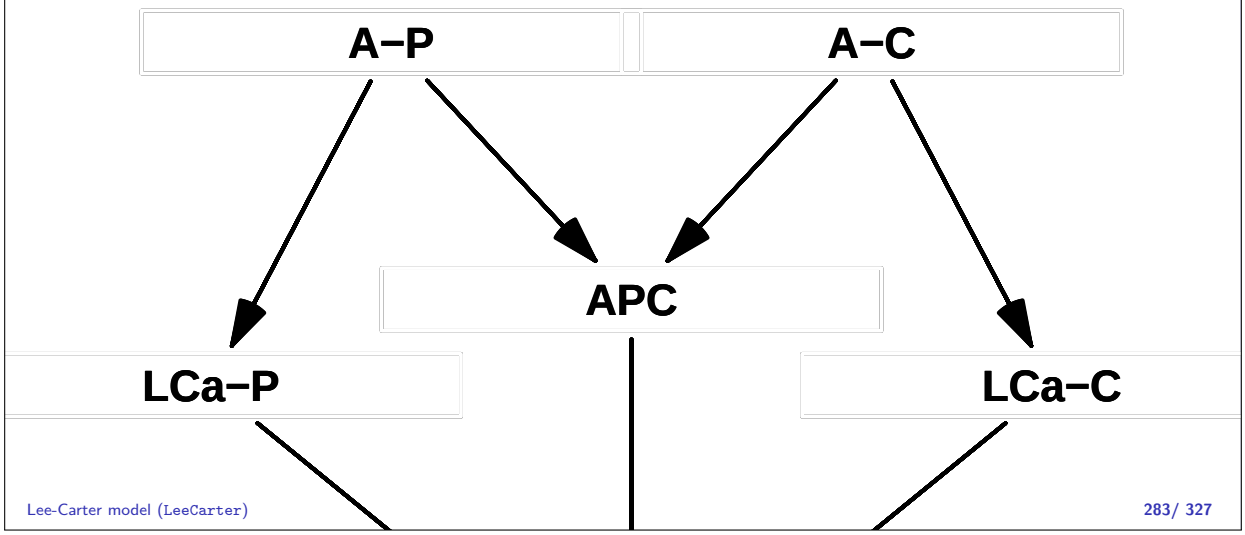

Lee-Carter with Epi



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 smalles **union** of Age-Period and Age-Cohort
- Extended Lee-Carter (from the `ilc` package)
  $\log\big(\lambda(a,p)\big) = f(a) + b(a) \times k(p) + c(a)m(p-a)$
  is the union of all of these.

Lee-Carter and the APC-model



Fit L-Ca models in `Epi` I

```
> LCa.P <- LCa.fit( Mlc, ref.b=60, ref.t=1980 )

LCa.fit convergence in  11  iterations, deviance: 8566.554 on 6084 d.f.

> LCa.C <- LCa.fit( Mlc, ref.b=60, ref.t=1980, model="C", maxit=200, eps=10e-4 )

LCa.fit convergence in  95  iterations, deviance: 8125.318 on 6084 d.f.

> ( a.kn <- LCa.P$a.kn )

8.333333%       25% 41.66667% 58.33333%       75% 91.66667%
       53        60        65        69        74        80

> LCa.C$a.kn

8.333333%       25% 41.66667% 58.33333%       75% 91.66667%
       53        60        65        69        74        80
```

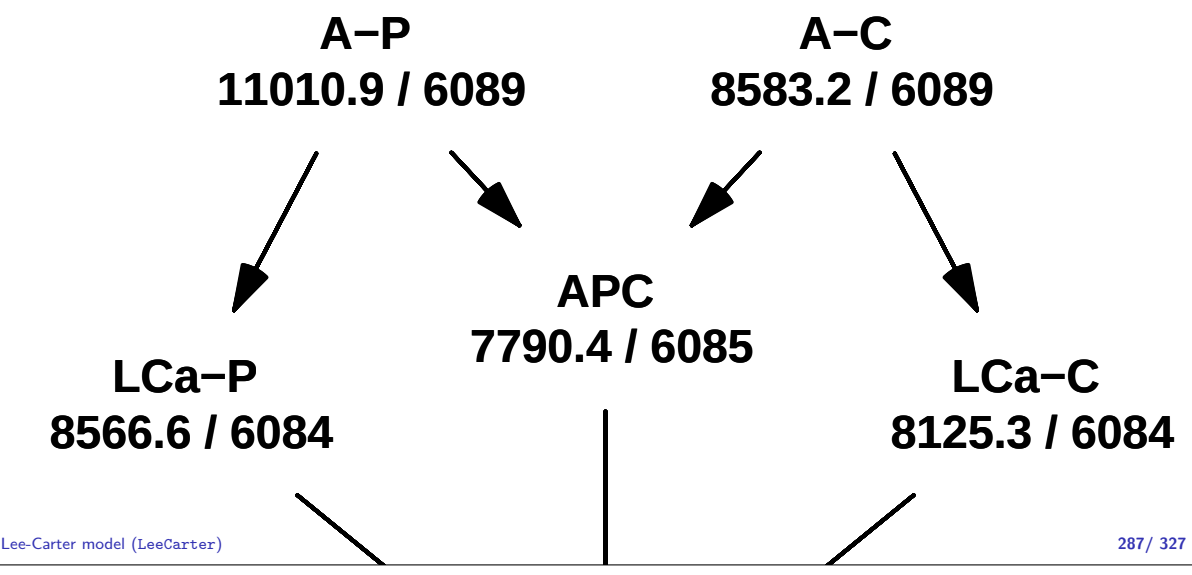
Fit L-Ca models in Epi II

```
> ( p.kn <- LCa.P$t.kn )

8.333333%       25% 41.66667% 58.33333%       75% 91.66667%
     1959      1971      1979      1985      1992      2000

> ( c.kn <- LCa.C$t.kn )

8.333333%       25% 41.66667% 58.33333%       75% 91.66667%
     1893      1904      1911      1918      1925      1935

> AP  <- glm( D ~ Ns(A,knots=a.kn)+Ns(P,knots=p.kn),
+                 offset=log(Y), family=poisson, data=Mlc )
> AC  <- glm( D ~ Ns(A,knots=a.kn)+                 Ns(P-A,knots=c.kn),
+                 offset=log(Y), family=poisson, data=Mlc )
> APC <- glm( D ~ Ns(A,knots=a.kn)+Ns(P,knots=p.kn)+Ns(P-A,knots=c.kn),
+                 offset=log(Y), family=poisson, data=Mlc )
> c( AP$deviance, AP$df.res )

[1] 11010.88  6089.00
```


Fit L-Ca models in Epi III

```
> c( AC$deviance, AC$df.res )

[1] 8583.249 6089.000

> c( APC$deviance, APC$df.res )

[1] 7790.446 6085.000

> c( LCa.P$dev, LCa.P$df )

[1] 8566.554 6084.000

> c( LCa.C$dev, LCa.C$df )

[1] 8125.318 6084.000
```


Fit L-Ca models in Epi IV



APC-models for several datasets

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APC2

Two APC-models

- APC-models for two sets of rates (men/women, types of events):

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

- Rate-ratio also an APC-model:

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

- Modeled separately and the ratio effecs reported as any other APC-model.

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 0 1 1 1 1 ...
 $ p    : int  1943 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 0 ...
```

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/10^5 )[,c("A","P","D","Y","hist")]
```



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

 ----------------------------
 Histology         D       Y
 ----------------------------
 Sem          4708.00 1275.25
 nS           3632.00 1275.25
 Oth           466.00 1275.25

 Total        8806.00 3825.76
 ----------------------------
```

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


```
> 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

                  Resid. Df Resid. Dev Df Deviance  Pr(>Chi)
Age                    9712     6845.8
Age-drift              9711     6255.1  1   590.70 < 2.2e-16
Age-Cohort             9705     6210.0  6    45.09 4.500e-08
Age-Period-Cohort      9699     6184.1  6    25.90 0.0002323
Age-Period             9705     6241.9 -6   -57.75 1.289e-10
Age-drift              9711     6255.1 -6   -13.24 0.0393950
```

```
> 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

                   Resid. Df Resid. Dev Df Deviance  Pr(>Chi)
Age                     9712     6316.4
Age-drift               9711     5619.1  1   697.29 < 2.2e-16
Age-Cohort              9705     5575.6  6    43.51 9.243e-08
Age-Period-Cohort       9699     5502.9  6    72.75 1.117e-13
Age-Period              9705     5550.8 -6   -47.91 1.229e-08
Age-drift               9711     5619.1 -6   -68.34 8.945e-13

> apc.Sem$Drift

                 exp(Est.)     2.5%    97.5%
APC (D-weights)  1.023586 1.021563 1.025614
A-d              1.023765 1.021773 1.025761
```



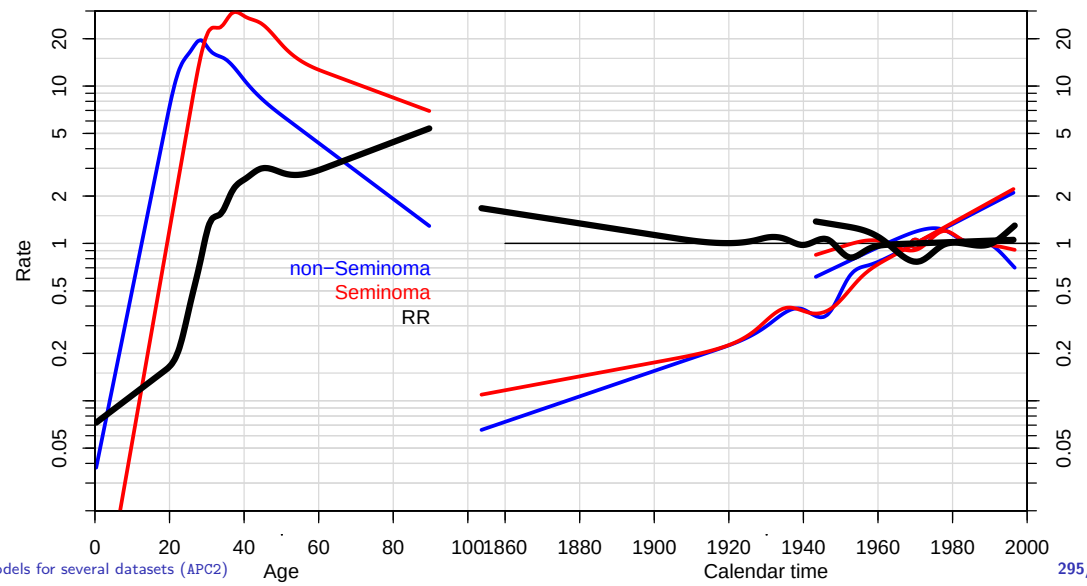
```
> apc.nS$Drift

                 exp(Est.)     2.5%    97.5%
APC (D-weights)  1.029438 1.026870 1.032013
A-d              1.030162 1.027799 1.032531


> plot( apc.nS, col="blue" )

cp.offset    RR.fac
     1750         1

> lines( apc.Sem, col="red" )
> matlines( apc.nS$Age[,1], apc.Sem$Age[,2]/apc.nS$Age[,2],
+           lty=1, lwd=5, col="black" )
> pc.lines( apc.nS$Per[,1], apc.Sem$Per[,2]/apc.nS$Per[,2],
+           lty=1, lwd=5, col="black" )
> pc.lines( apc.nS$Coh[,1], apc.Sem$Coh[,2]/apc.nS$Coh[,2],
+           lty=1, lwd=5, col="black" )
> text( 90, 0.7, "non-Seminoma", col="blue", adj=1 )
> text( 90, 0.7^2, "Seminoma", col="red", adj=1 )
> text( 90, 0.7^3, "RR", col="black", adj=1 )
```

Analysis of two rates: Formal tests I

```
> Ma <- ns( A, df=15, intercept=TRUE )
> Mp <- ns( P, df=15 )
> Mc <- ns( P-A, df=20 )
> Mp <- detrend( Mp, P, weight=D )
> Mc <- detrend( Mc, P-A, weight=D )
>
> m.apc <- glm( D ~ -1 + Ma:type + Mp:type + Mc:type + offset( log(Y)), family=poi
> m.ap  <- update( m.apc, . ~ . - Mc:type + Mc )
> m.ac  <- update( m.apc, . ~ . - Mp:type + Mp )
> m.a   <- update( m.ap , . ~ . - Mp:type + Mp )
>
> anova( m.a, m.ac, m.apc, m.ap, m.a, test="Chisq")
Analysis of Deviance Table

Model 1: D ~ Mc + Mp + Ma:type + offset(log(Y)) - 1
Model 2: D ~ Mp + Ma:type + type:Mc + offset(log(Y)) - 1
Model 3: D ~ -1 + Ma:type + Mp:type + Mc:type + offset(log(Y))
Model 4: D ~ Mc + Ma:type + type:Mp + offset(log(Y)) - 1
```


Analysis of two rates: Formal tests II

```
Model 5: D ~ Mc + Mp + Ma:type + offset(log(Y)) - 1
  Resid. Df Resid. Dev    Df Deviance P(>|Chi|)
1     10737    10553.7
2     10718    10367.9    19    185.7 2.278e-29
3     10704    10199.6    14    168.3 1.513e-28
4     10723    10508.6   -19   -309.0 2.832e-54
5     10737    10553.7   -14    -45.0 4.042e-05
```


APC-model: Interactions

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Age-Period-Cohort models
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APC-int

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 are the timetrends.

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" )
dm <- dm[dm$cen=="D1: Denmark",]

# Define knots and points of prediction
n.A <- 5
n.C <- 8
n.P <- 5
pA  <- seq(1/(3*n.A),1-1/(3*n.A),,n.A )
pC  <- seq(1/(3*n.C),1-1/(3*n.C),,n.P )
pP  <- seq(1/(3*n.P),1-1/(3*n.P),,n.C )
c0  <- 1985
attach( dm, warn.conflicts=FALSE )
A.kn <- quantile( rep( A, D ), probs=pA[-c(1,n.A)] )
A.ok <- quantile( rep( A, D ), probs=pA[ c(1,n.A)] )
A.pt <- sort( A[match( unique(A), A )] )
C.kn <- quantile( rep( C, D ), probs=pC[-c(1,n.C)] )
C.ok <- quantile( rep( C, D ), probs=pC[ c(1,n.C)] )
C.pt <- sort( C[match( unique(C), C )] )
```


Analysis of DM-rates: Age×sex interaction III

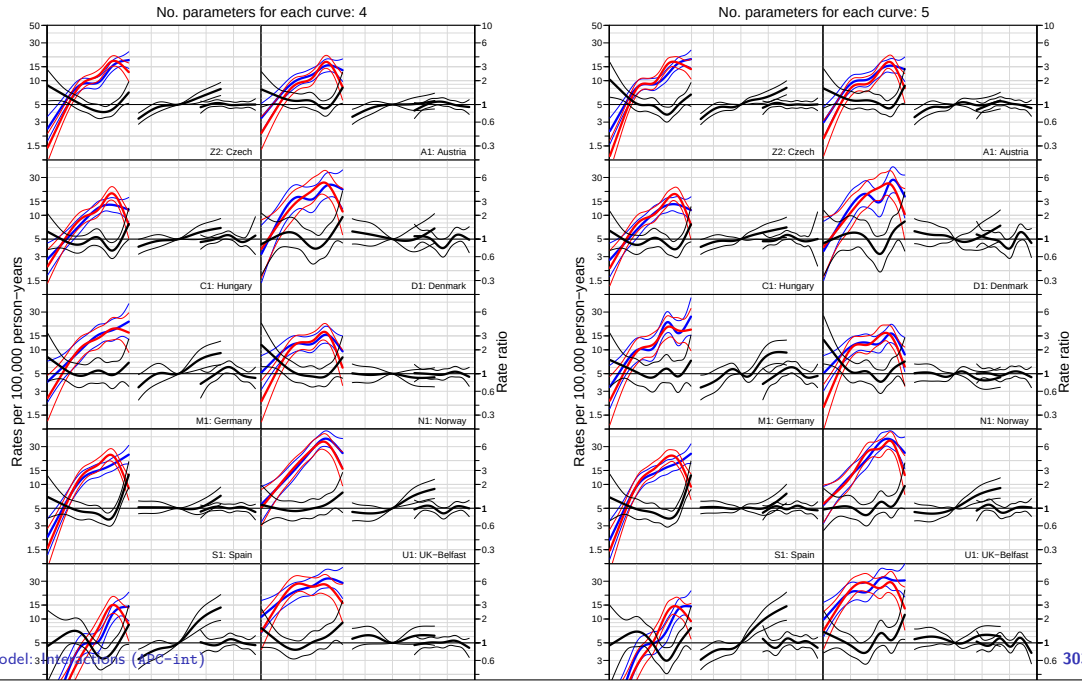
```
P.kn <- quantile( rep( P, D ), probs=pP[-c(1,n.P)] )
P.ok <- quantile( rep( P, D ), probs=pP[ c(1,n.P)] )
P.pt <- sort( P[match( unique(P), P )] )

# Age-cohort model with age-sex interaction
# The model matrices for the ML fit
Ma <-                       ns( A, kn=A.kn, Bo=A.ok, intercept=T )
Mc <- cbind( C-c0, detrend( ns( C, kn=C.kn, Bo=C.ok ), C, weight=D ) )
Mp <-              detrend( ns( P, kn=P.kn, Bo=P.ok ), P, weight=D )
# The prediction matrices
Pa <- Ma[match(A.pt,A),,drop=F]
Pc <- Mc[match(C.pt,C),,drop=F]
Pp <- Mp[match(P.pt,P),,drop=F]

# Fit the apc model by ML
apcs <- glm( D ~ Ma:sex - 1 + Mc + Mp +
                 offset( log (Y/10^5) ),
                 family=poisson,
                 data=dm )
summary( apcs )
```

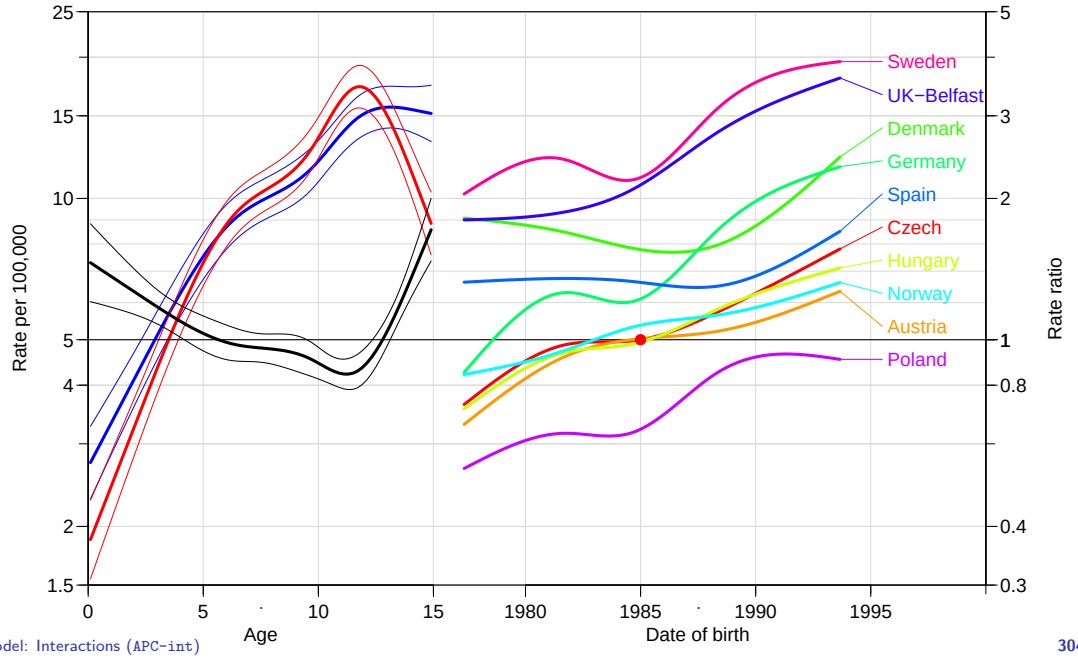
Analysis of DM-rates: Age×sex interaction IV

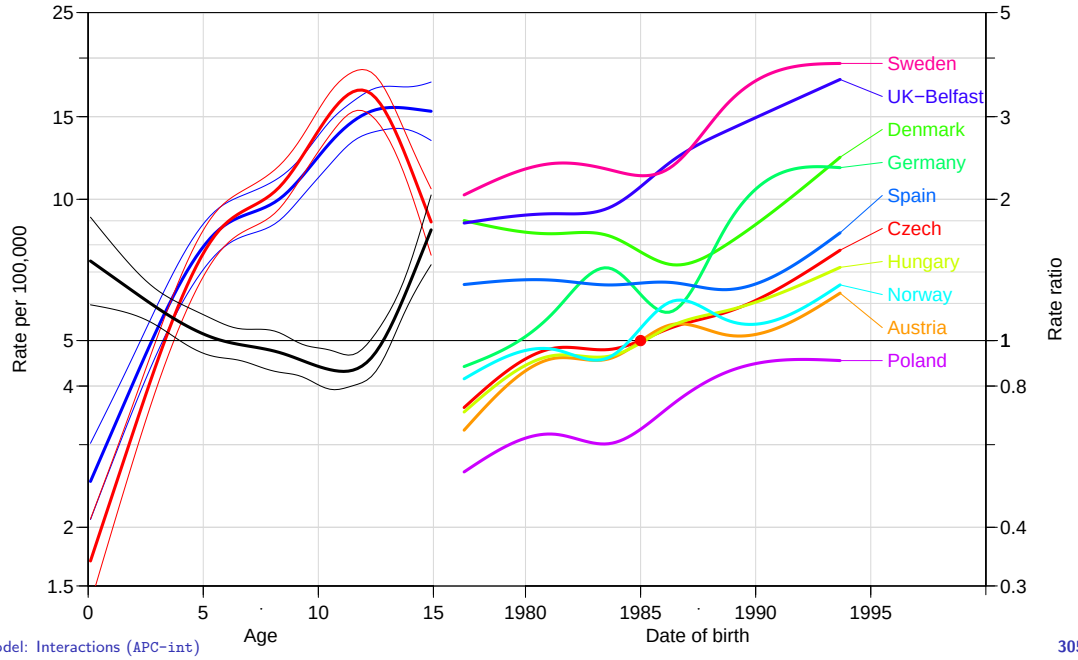
```
ci.lin( apcs )
ci.lin( apcs, subset="sexF", Exp=T)
ci.lin( apcs, subset="sexF", ctr.mat=Pa, Exp=T)

# Extract the effects
F.inc <- ci.lin( apcs, subset="sexF", ctr.mat=Pa, Exp=T)[,5:7]
M.inc <- ci.lin( apcs, subset="sexM", ctr.mat=Pa, Exp=T)[,5:7]
MF.RR <- ci.lin( apcs, subset=c("sexM","sexF"), ctr.mat=cbind(Pa,-Pa), Exp=T)[,5:7
 c.RR <- ci.lin( apcs, subset="Mc", ctr.mat=Pc, Exp=T)[,5:7]
 p.RR <- ci.lin( apcs, subset="Mp", ctr.mat=Pp, Exp=T)[,5:7]

# 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
fr <- 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),
```


Analysis of DM-rates: Age×sex interaction V

```
                rr.ref=5,
                   gap=1,
              col.grid=gray(0.9),
                 a.txt="",
                cp.txt="",
                 r.txt="",
                rr.txt="" )

# Draw the estimates
matlines( A.pt, M.inc, lwd=c(3,1,1), lty=1, col="blue" )
matlines( A.pt, F.inc, lwd=c(3,1,1), lty=1, col="red" )
matlines( C.pt - fr[1], c.RR * fr[2],
          lwd=c(3,1,1), lty=1, col="black" )
matlines( P.pt - fr[1], p.RR * fr[2],
          lwd=c(3,1,1), lty=1, col="black" )
matlines( A.pt, MF.RR * fr[2],
          lwd=c(3,1,1), lty=1, col=gray(0.6) )
abline(h=fr[2])
```





Predicting future rates

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predict

Prediction of future rates

Model:

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

- Why not just extend the estimated functions into the future?
- The parametrization curse — the model as stated is not uniquely parametrized.
- Predictions from the model must be invariant under reparametrization.

Identifiability

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

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

Parametrization invariance

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

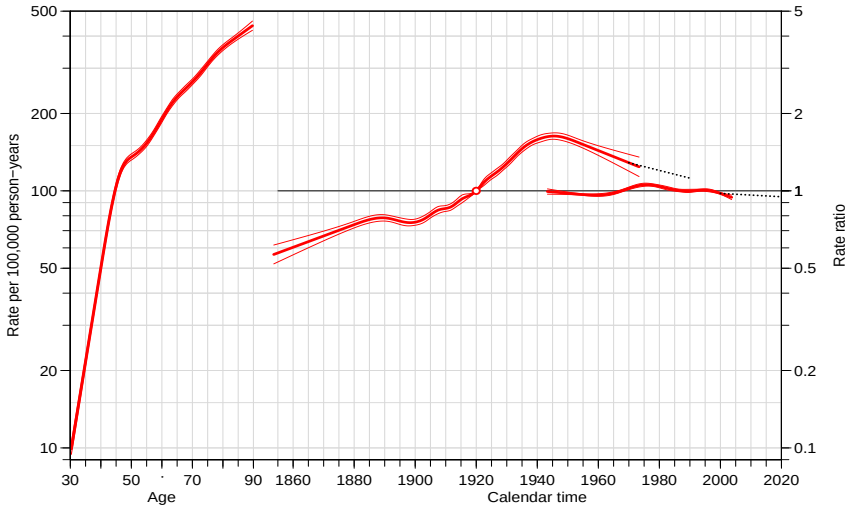
$$\begin{aligned}\text{pred}\big(g(p) + \gamma p\big) &= \text{pred}\big(g(p)\big) + \gamma p \\ \text{pred}\big(h(c) - \gamma c\big) &= \text{pred}\big(h(c)\big) - \gamma c\end{aligned}$$

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

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.

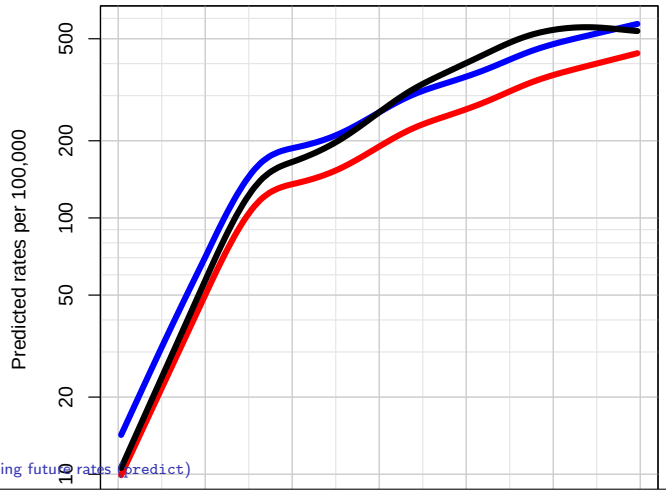
Example: Breast cancer in Denmark



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.

Bresat cancer prediction



Predicted age-specific breast cancer rates at 2020 (black),

in the 1950 cohort (blue),

and the estimated age-effects (red).

Continuous outcomes

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`cont`

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:

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

- . . . or more precisely:

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

APC-model for quantitative outcomes

- Model:

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

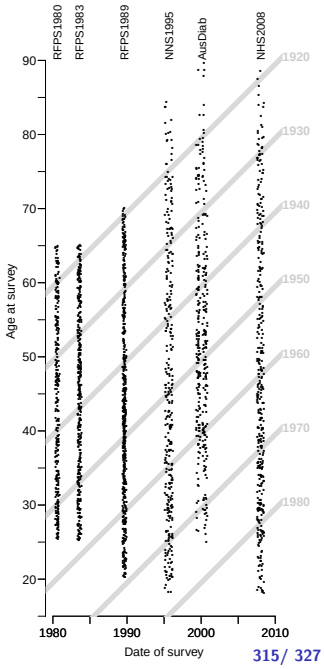
- But the identification problem is still the same:

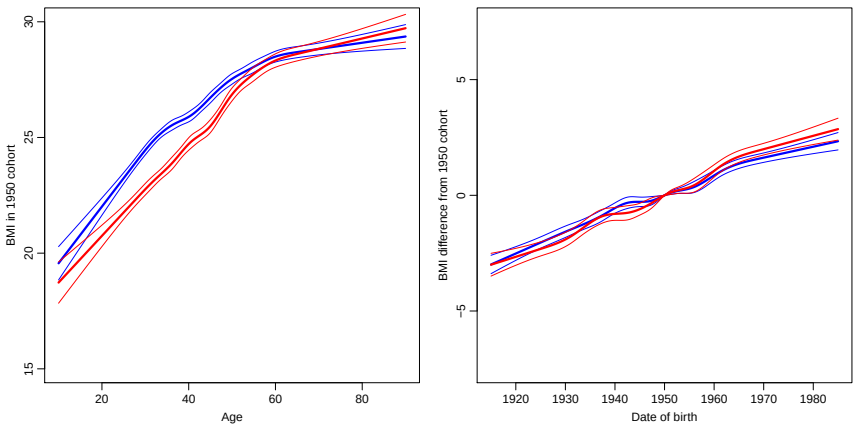
$$c(i) = p(i) - a(i), \quad \forall i$$

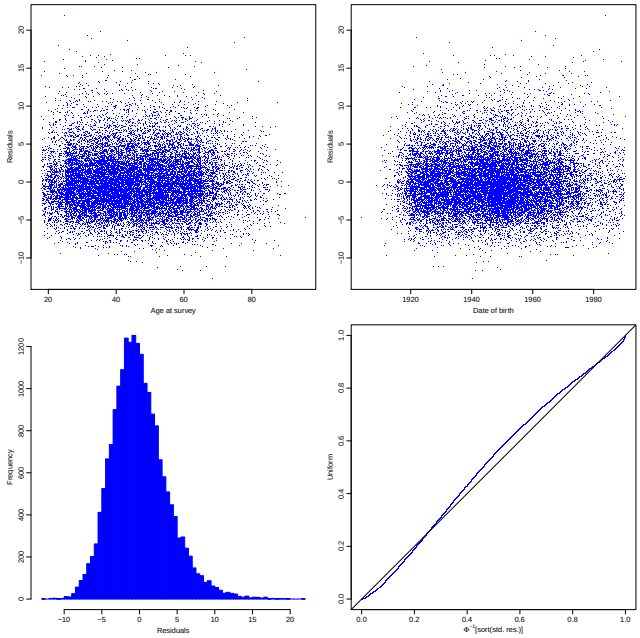
- But the same machinery applies with extraction of the effects
- — and plotting of predictions of
  - $\mathrm{E}(\text{BMI})$
  - quantiles of BMI

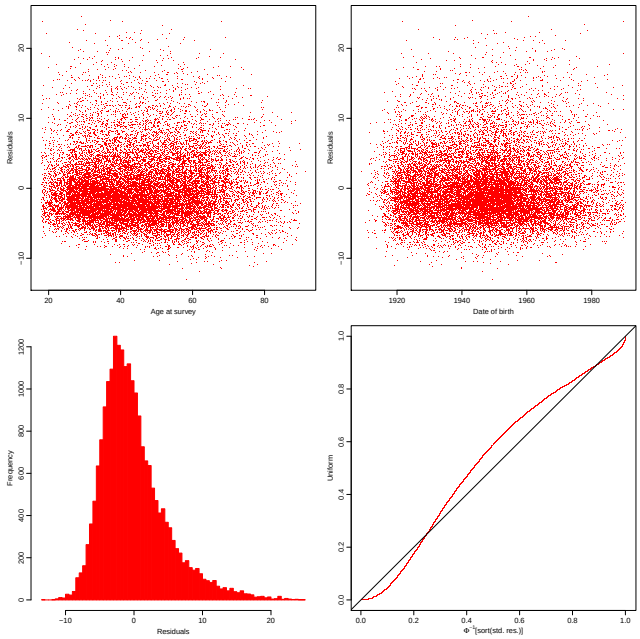
APC-model for quantitative outcomes

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






Residuals
Age at survey
Date of birth
Frequency
Uniform
Φ⁻¹[sort(std. res.)]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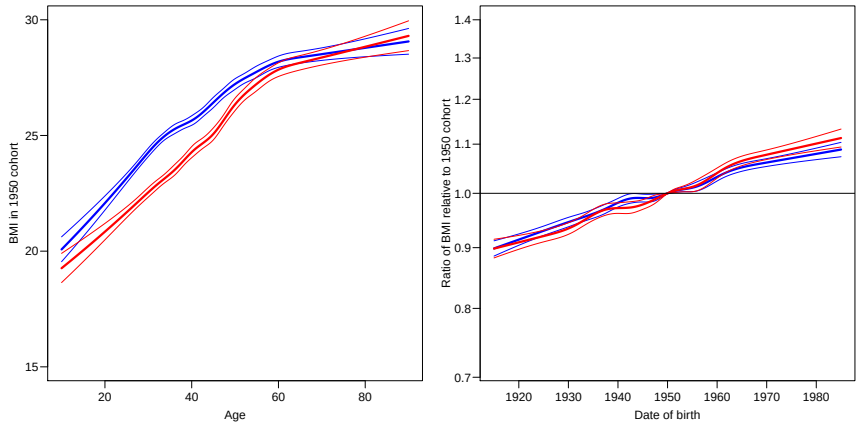
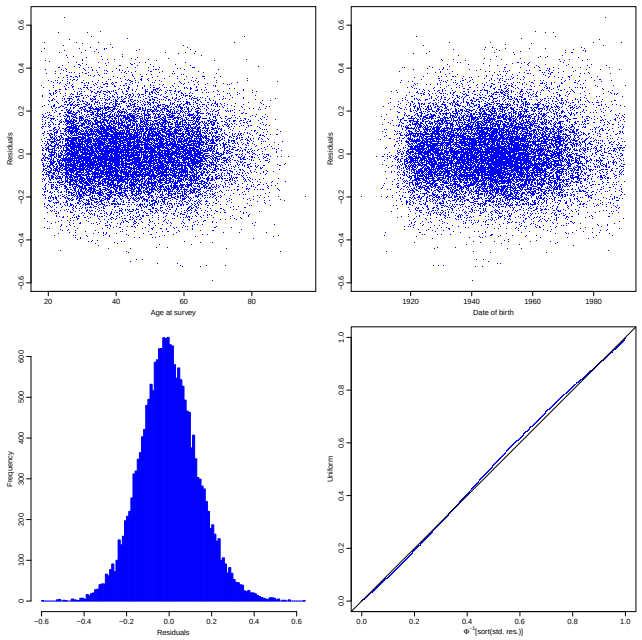
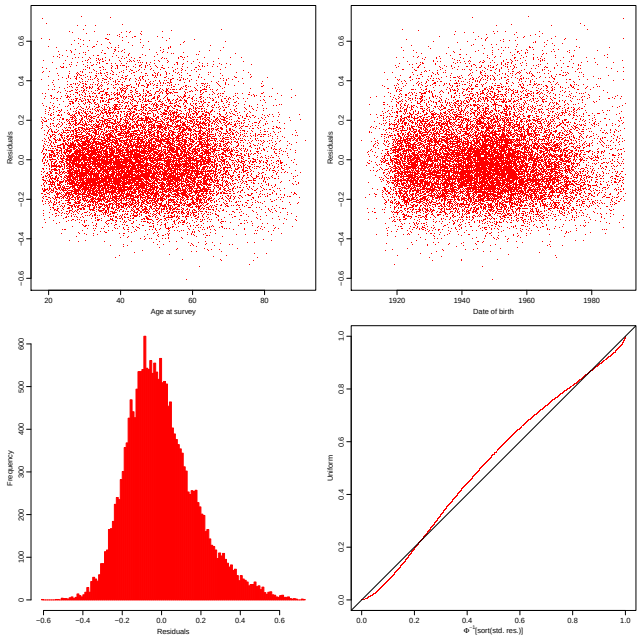
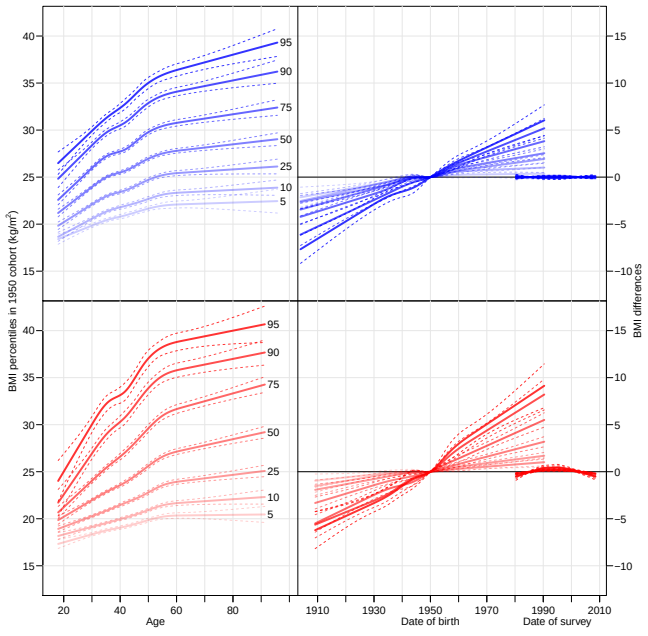
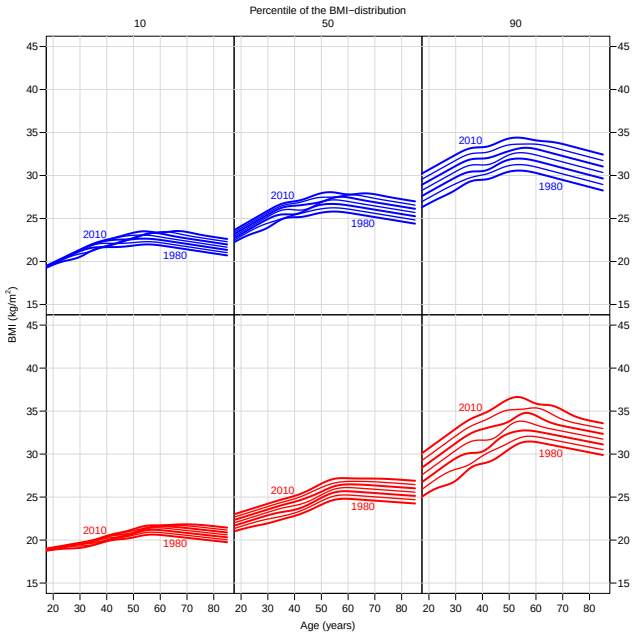
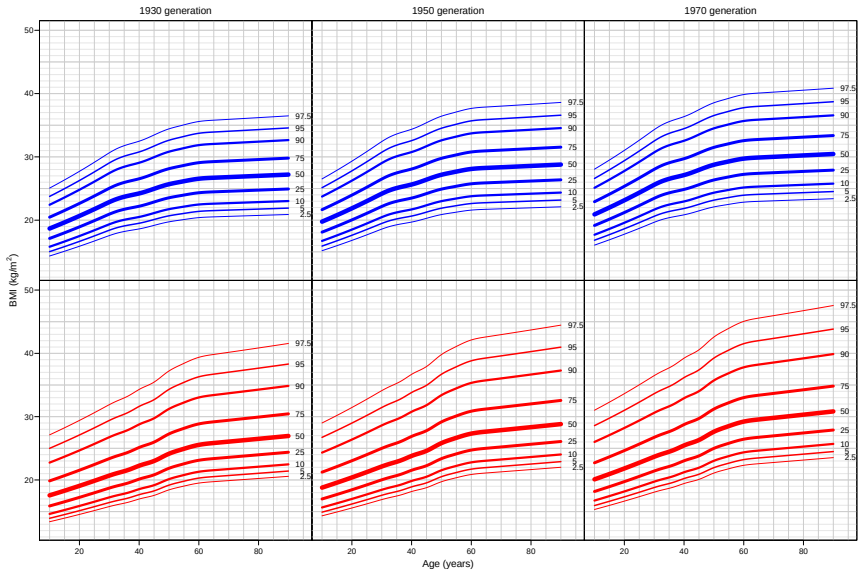

BMI in 1950 cohort
Age
Ratio of BMI relative to 1950 cohort
Date of birth

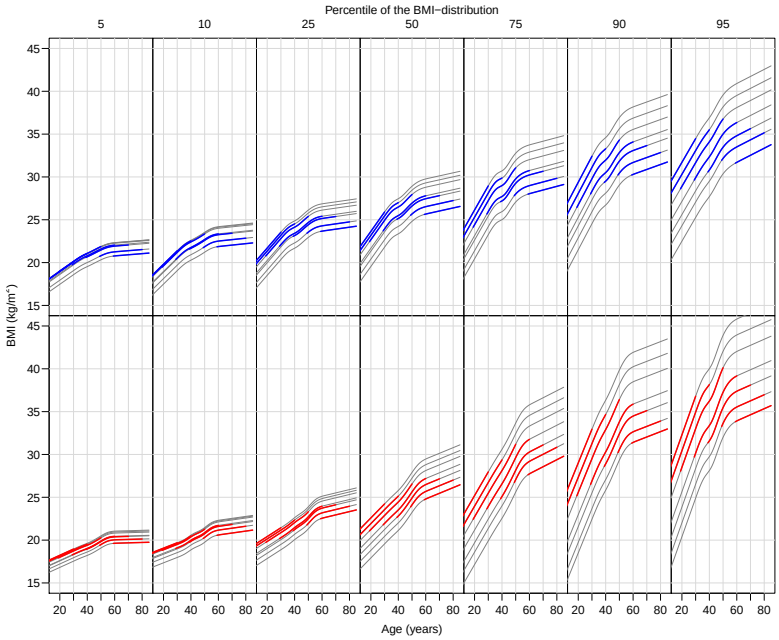

Residuals
Age at survey
Date of birth
Frequency
Residuals
Uniform
Φ⁻¹[sort(std. res.)]

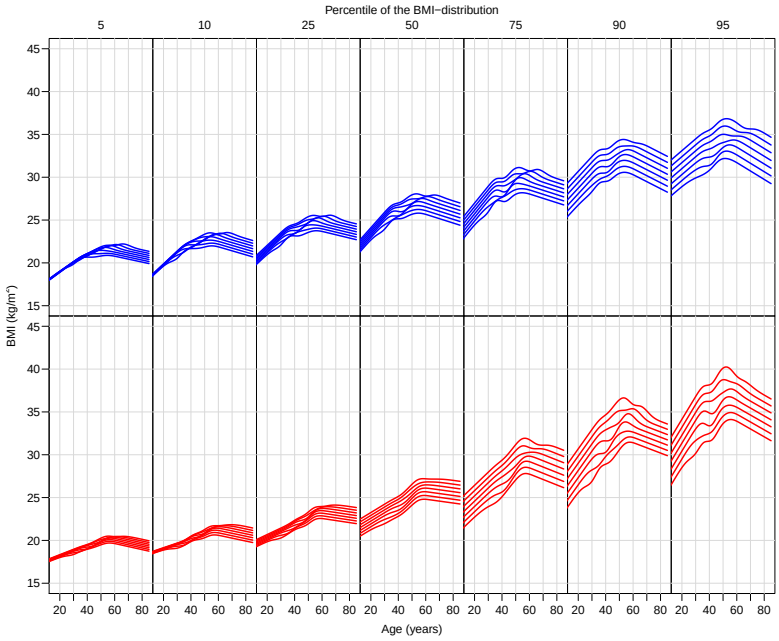

Residuals
Age at survey
Date of birth
Frequency
Residuals
Uniform
Φ⁻¹[sort(std. res.)]


BMI percentiles in 1950 cohort (kg/m²)
BMI differences
95
90
75
50
25
10
5
Age
Date of birth
Date of survey


Percentile of the BMI−distribution
10
50
90
BMI (kg/m²)
Age (years)
2010
1980


1930 generation
1950 generation
1970 generation
BMI (kg/m²)
Age (years)
97.5
95
90
75
50
25
10
5
2.5


Percentile of the BMI−distribution
5
10
25
50
75
90
95
BMI (kg/m²)
Age (years)


Percentile of the BMI−distribution
5
10
25
50
75
90
95
BMI (kg/m²)
Age (years)

References