Statistical Analysis in the Lexis Diagram: Age-Period-Cohort models

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March 2009
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Introduction
Monday 23rd, morning

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Age-Period-Cohort models
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Welcome

- Purpose of the course:
  - Knowledge about APC-models
  - Technincal knowledge of handling them
  - insight in the basic survival concepts
- Remedies of the course:
  - Lectures with handouts (BxC)
  - Practicals with suggested solutions (BxC + EG)

Scope of the course

- Rates as observed in populations — disease registers for example.
- Understanding of survival analysis (statistical analysis of rates) is needed — that is the content of much of the first day.
- Besides the concepts the practical understanding of the actual computations (in R) are emphasized.
- There is a section in the practicals: "Probability concepts in follow-up studies"

About the lectures

- Please interrupt:
  Most likely I did a mistake or left out a crucial argument.
- The handpout are not perfect — please comment on them, prospective students would benefit from it.
- There is a time-schedule in the practicals.
  I 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 the net; but we also have them on USB-sticks.
- 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 R-weave?)
- A minor bug in `apc.fit`, `apc.plot` and `apc.frame` is fixed in `Epi 1.0.11`

Rates and Survival
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Survival data

Persons enter the study at some date.

Persons exit at a later date, either dead or alive.

Observation:
Actual time span to death ("event")
or
Some time alive ("at least this long")

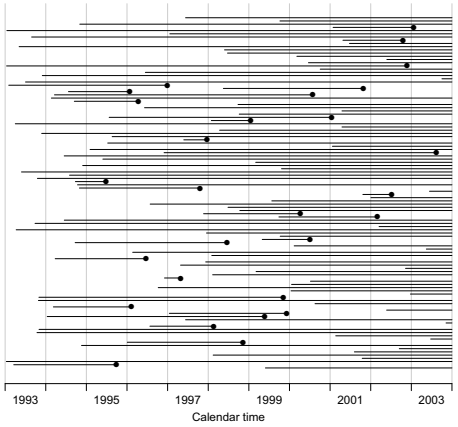
Examples of time-to-event measurements

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

Each line a person

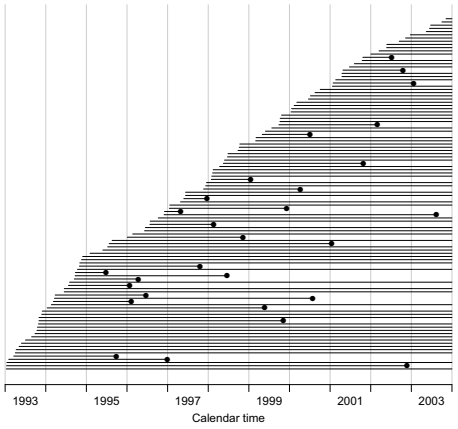
Each blob a death

Study ended at 31 Dec. 2003

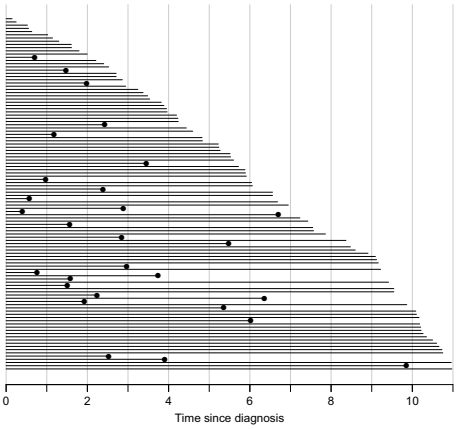


Ordered by date of entry

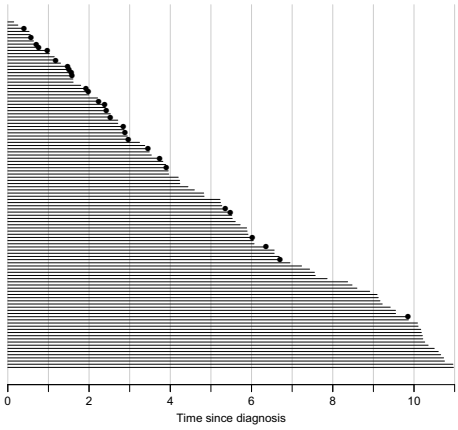
Most likely the order in your database.



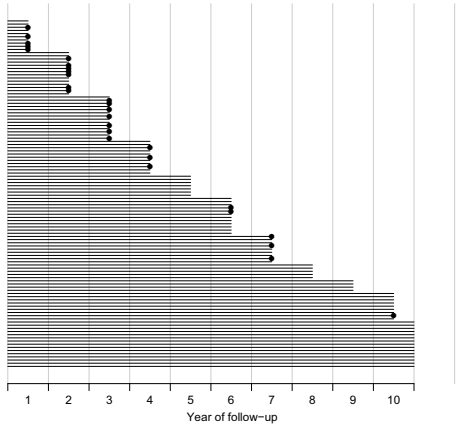
Timescale changed to "Time since diagnosis".



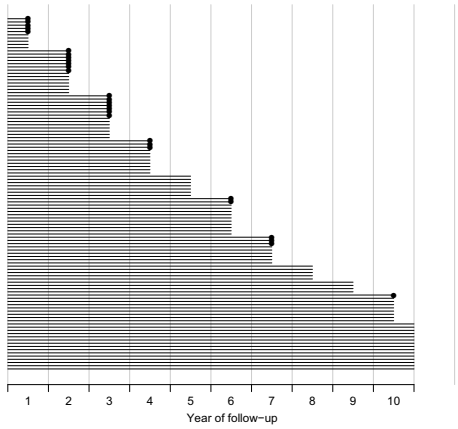
Patients ordered by survival time.



Survival times grouped into bands of survival.



Patients ordered by survival status within each band.



Survival after Cervix cancer

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

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

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

Life-table estimator.

Survival function

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

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

Distribution is characterized by the survival function:

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

Intensity or rate

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

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

Theoretical counterpart of a **rate**.

Relationships

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

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

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

Rate and survival

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

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

Note: A cumulative measure requires an origin!

Observed survival and rate

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

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

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

  $$D/Y$$

  D: no. events, Y no of person-years, in a prespecified time-frame.

Empirical rates for individuals

At the *individual* level we introduce the **empirical rate:** (d, y),
— no. of events ($d \in \{0, 1\}$) during y risk time.

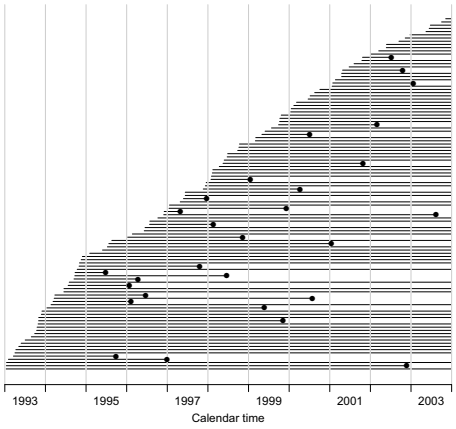
Each person contributes several obs. of (d, y).

Empirical rates are **responses** in survival analysis.

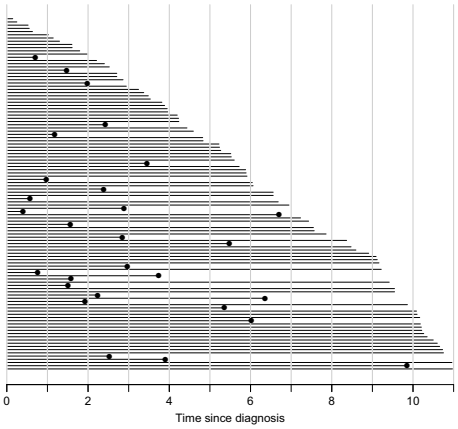
The timescale is a **covariate** — varies across empirical rates from one individual:
Age, calendar time, time since diagnosis.

Don't confuse timescale with y — difference between two points on **any** timescale we may choose.

Empirical rates by calendar time.



Empirical rates by time since diagnosis.



Two timescales

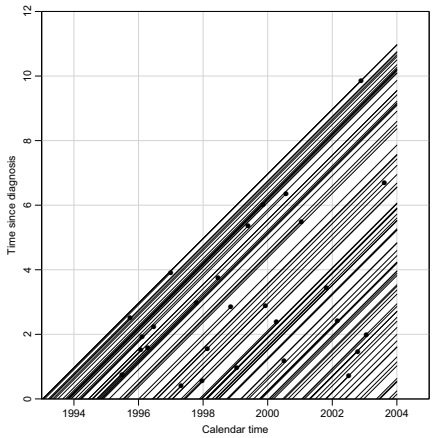
Note that we actually have two timescales:

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

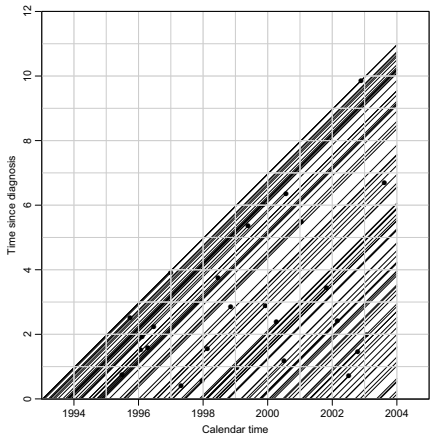
These can be shown simultaneously in a Lexis diagram.

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 from one person

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

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

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

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

Likelihood for an empirical rate

Model: the rate is constant in the interval we are looking at. The interval should sufficiently small for this assumption to be reasonable.

If $\pi = 1 - \mathrm{e}^{-\lambda y}$ is the death probability:

$$\begin{aligned}L(\lambda) &= \mathrm{P}\{d \text{ events during } y \text{ time }\} = \pi^d(1-\pi)^{1-d} \\ &= (1-\mathrm{e}^{-\lambda y})^d(\mathrm{e}^{-\lambda y})^{1-d} \\ &= \left(\frac{1-\mathrm{e}^{-\lambda y}}{\mathrm{e}^{-\lambda y}}\right)^d(\mathrm{e}^{-\lambda y}) \approx (\lambda y)^d\mathrm{e}^{-\lambda y}\end{aligned}$$

since the first term is equal to $\mathrm{e}^{-\lambda y} - 1 \approx \lambda y$.

Log-likelihood:

$$l(\lambda) = d\log(\lambda y) - \lambda y = d\log(\lambda) + d\log(y) - \lambda y$$

The term $d\log(y)$ does not include λ, so the relevant part of the log-likelihood is:

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

Likelihood

Probability of the data and the parameter:

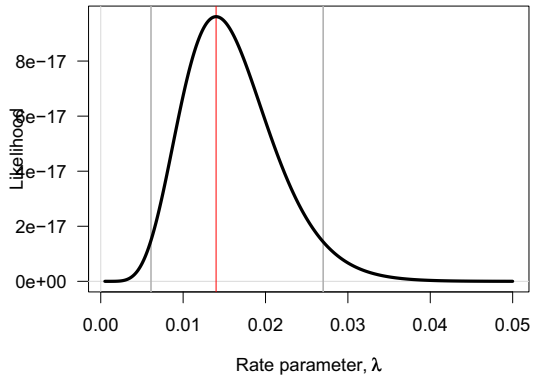
Assuming the rate (intensity) is constant, λ, the probability of observing 7 deaths in the course of 500 person-years:

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

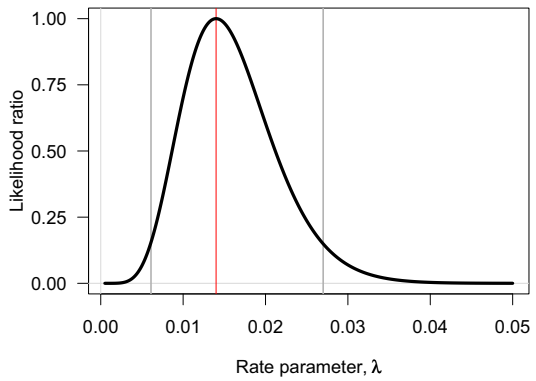
Best guess of λ is where this function is as large as possible.

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

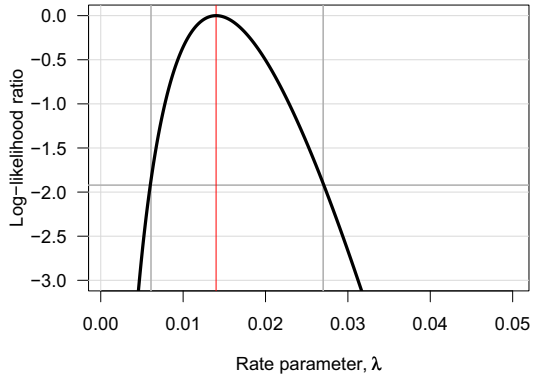
Likelihood function



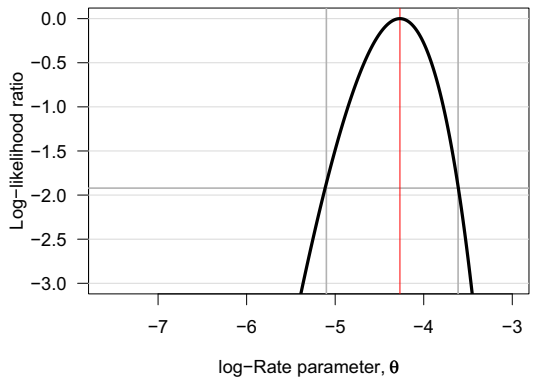
Likelihood-ratio function



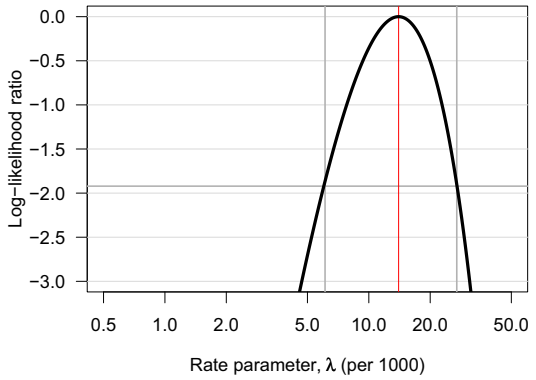
Log-likelihood ratio



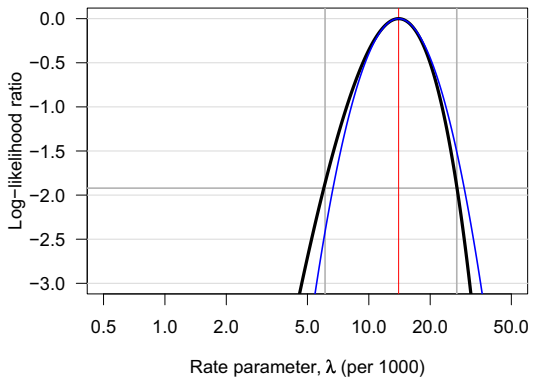
Log-likelihood ratio, $\theta = \log(\lambda)$



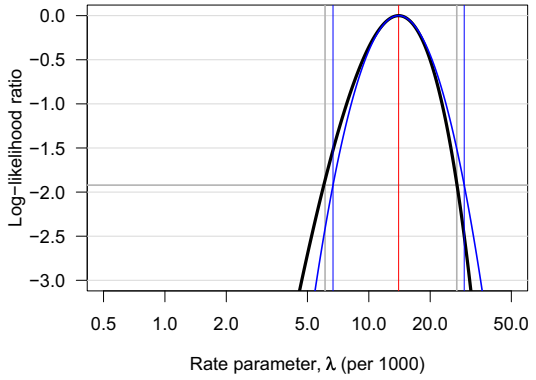
Log-likelihood ratio



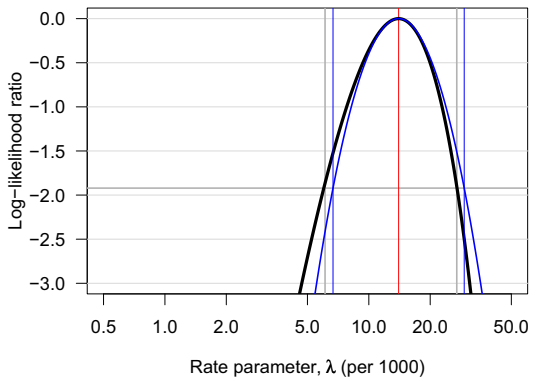
Log-likelihood ratio



Log-likelihood ratio



Log-likelihood ratio



$\hat{\lambda} = 7/500 = 14 \quad \hat{\lambda} \overset{\times}{\div} \exp(1.96/\sqrt{7}) = (6.7, 29.4)$

Poisson likelihood

The contributions from **one** individual:

$$d_t \log(\lambda(t)) - \lambda(t) y_t, \quad t = 1, \ldots, T$$

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

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

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

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

Information about $\theta = \log(\lambda)$:

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

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

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:

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

Exercise

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

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

Exercise – solution

The rate is computed as:

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

The confidence interval is computed as:

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

per 1000 person-years.

Ratio of two rates

If we have observations two rates λ_1 and λ_0, based on (D_1, Y_1) and (D_0, Y_0) the variance of the difference of the ratio of the rates, 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-ration between group 1 and 0 with a 95% c.i.

Exercise – solution

The rate-ratio is computed as:

$$\begin{aligned} \mathrm{RR} &= \hat\lambda_1/\hat\lambda_0 = (D_1/Y_1)/(D_0/Y_0) \\ &= (28/632.3)/(17/843.7) = 0.0443/0.0201 = 2.19 \end{aligned}$$

The 95% confidence interval is computed as:

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

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

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

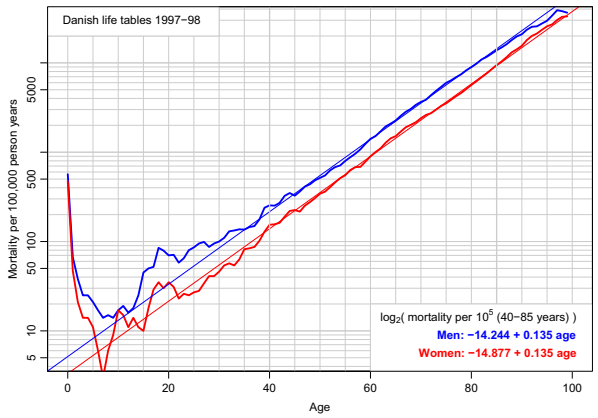
and hence the death probability:

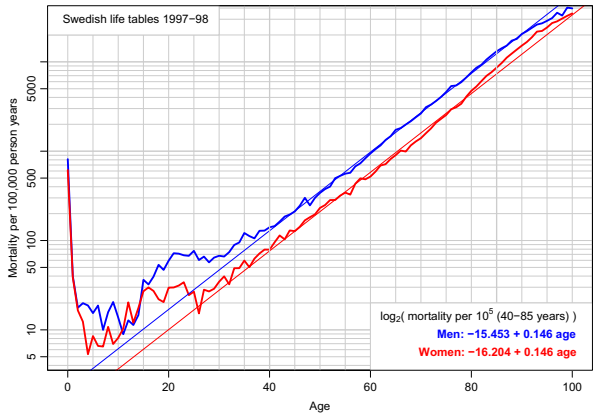
$$p_i = 1 - \exp -\lambda_i \ell_i = 1 - \exp\left(-\frac{d_i}{(n_i - d_i/2 - l_i/2)}\right)$$

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

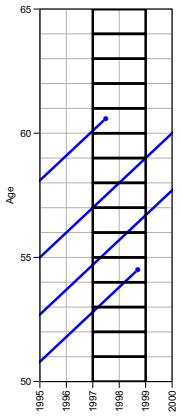
Based on the previous slides answer the following for both Danish and Swedish lifetables:

- 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**.

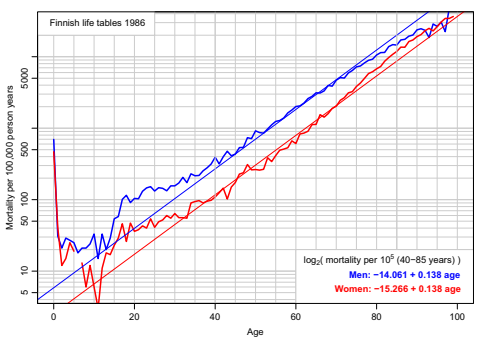
It is the **population** experience:

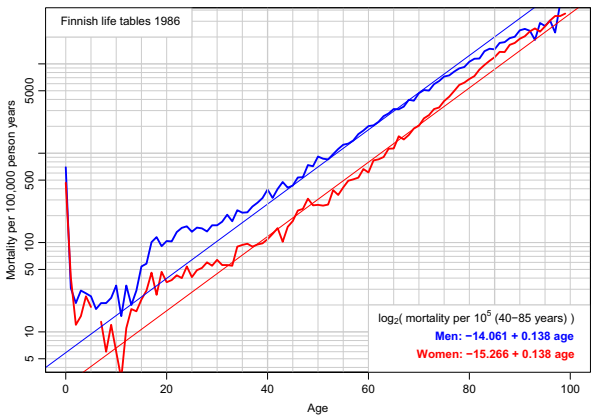
- D: Deaths (events).
- Y: Person-years (risk time).

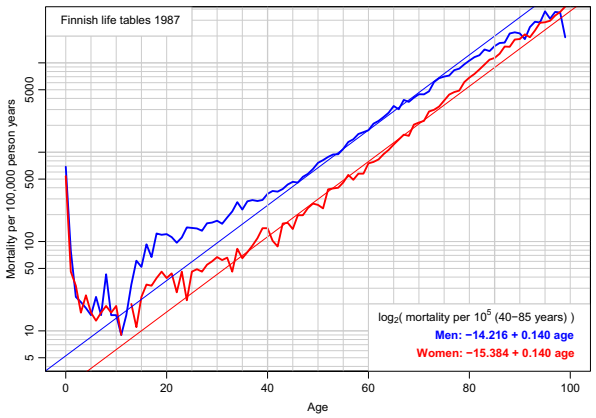
The classical lifetable analysis compiles these for prespecified intervals of age, and computes age-specific mortality **rates**.

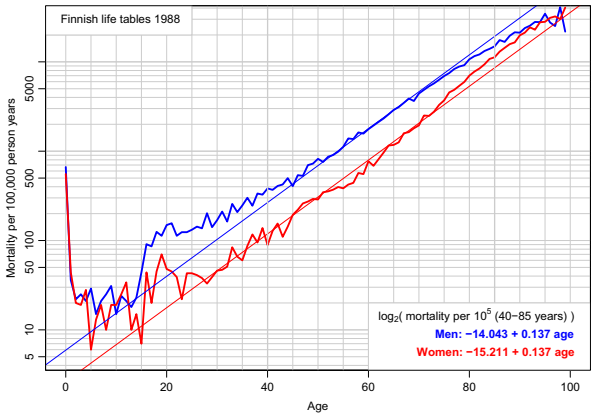
Data are collected cross-sectionally, but interpreted longitudinally.

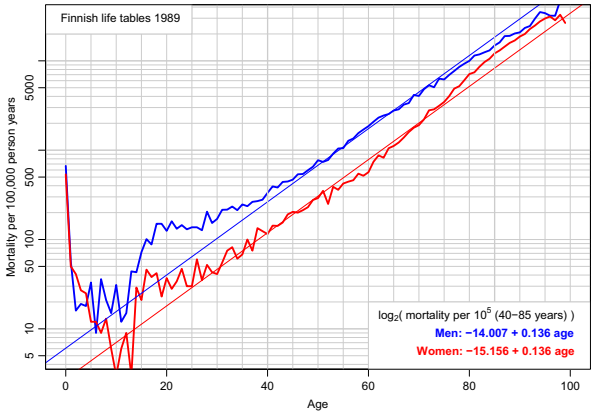
Rates vary over time:

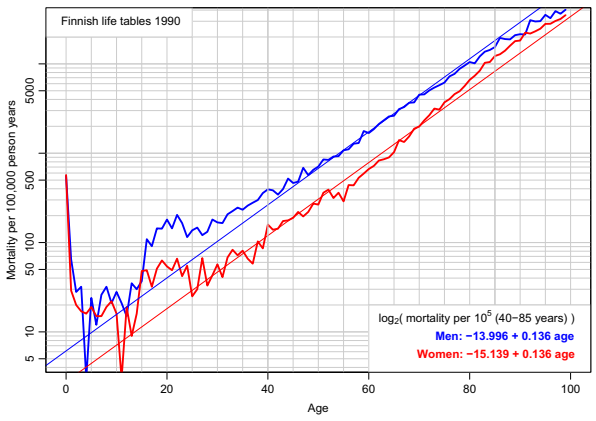


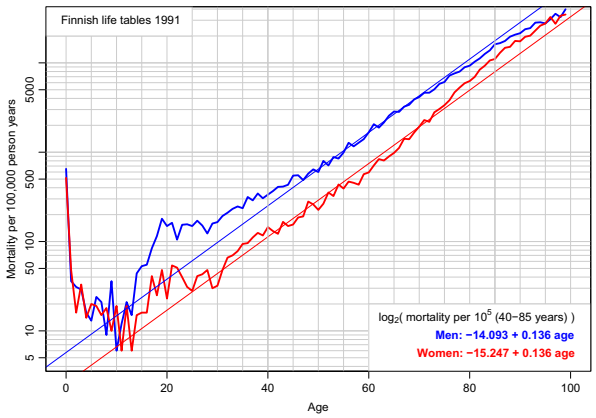


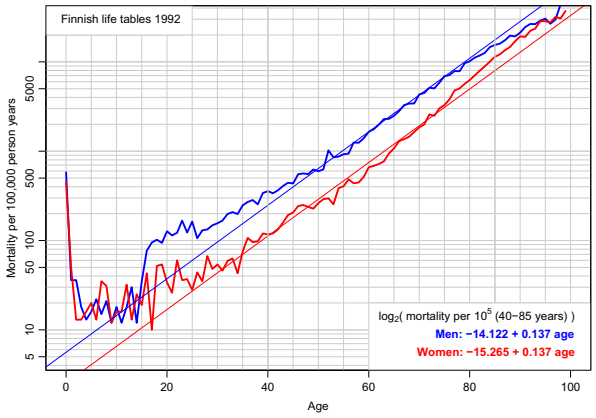


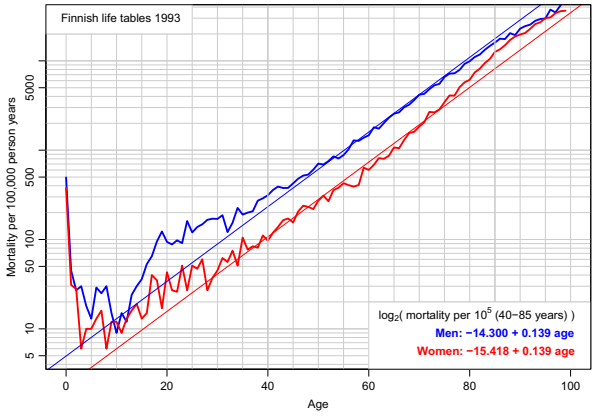


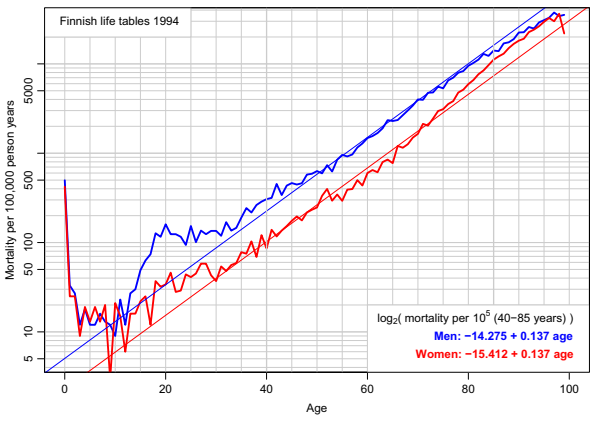


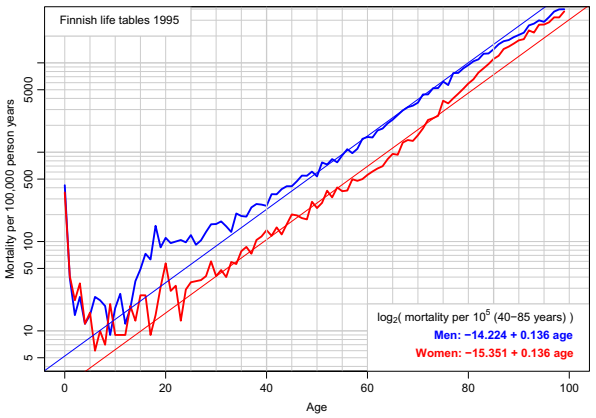

Finnish life tables 1990
Mortality per 100,000 person years
5
10
50
100
500
5000
0
20
40
60
80
100
Age
log2(mortality per 10^5 (40−85 years))
Men: −13.996 + 0.136 age
Women: −15.139 + 0.136 age

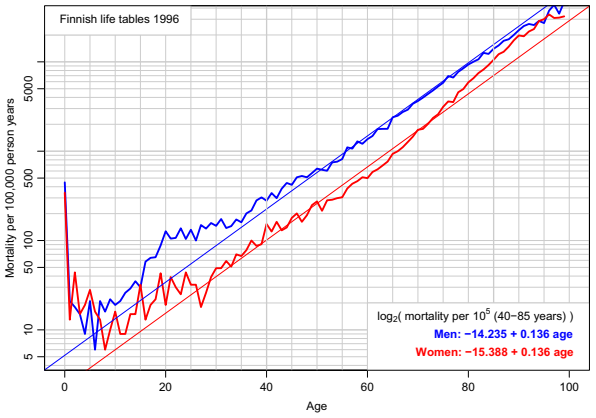

Finnish life tables 1991
Mortality per 100,000 person years
5
10
50
100
500
5000
0
20
40
60
80
100
Age
log2(mortality per 10^5 (40−85 years))
Men: −14.093 + 0.136 age
Women: −15.247 + 0.136 age

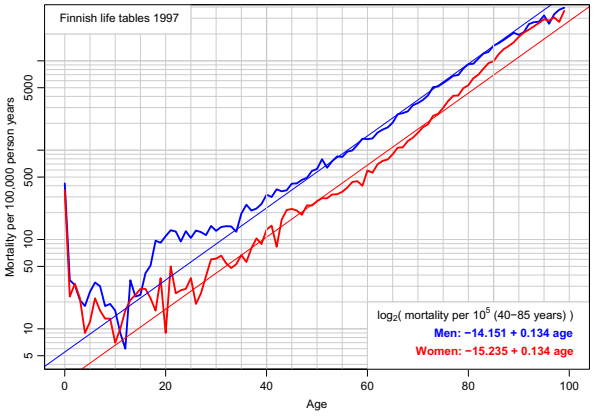

Finnish life tables 1992
Mortality per 100,000 person years
5
10
50
100
500
5000
0
20
40
60
80
100
Age
log2(mortality per 10^5 (40−85 years))
Men: −14.122 + 0.137 age
Women: −15.265 + 0.137 age

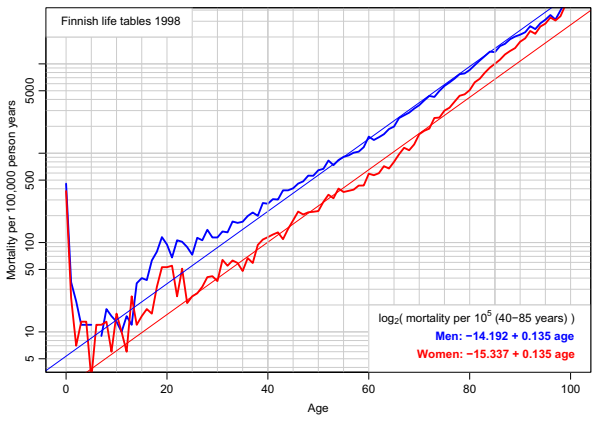

Finnish life tables 1993
Mortality per 100,000 person years
5
10
50
100
500
5000
0
20
40
60
80
100
Age
log2(mortality per 10^5 (40−85 years))
Men: −14.300 + 0.139 age
Women: −15.418 + 0.139 age

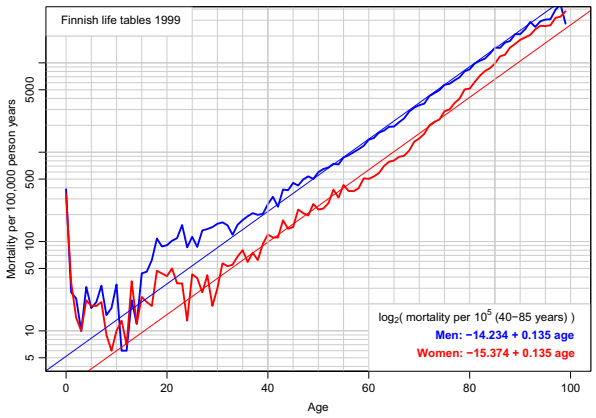

Finnish life tables 1994
Mortality per 100,000 person years
5
10
50
100
500
5000
0
20
40
60
80
100
Age
log2(mortality per 10^5 (40−85 years))
Men: −14.275 + 0.137 age
Women: −15.412 + 0.137 age

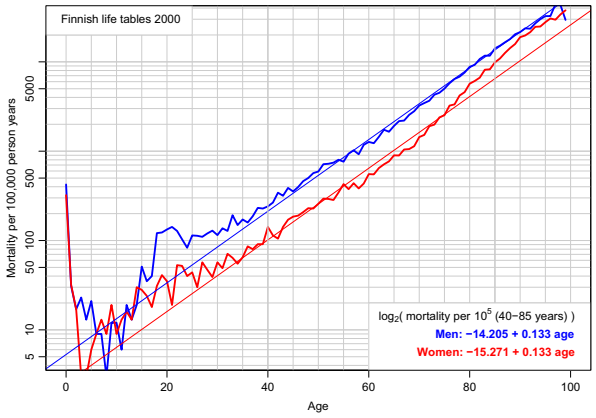

Finnish life tables 1995
Mortality per 100,000 person years
5
10
50
100
500
5000
0
20
40
60
80
100
Age
log2(mortality per 10^5 (40−85 years))
Men: −14.224 + 0.136 age
Women: −15.351 + 0.136 age

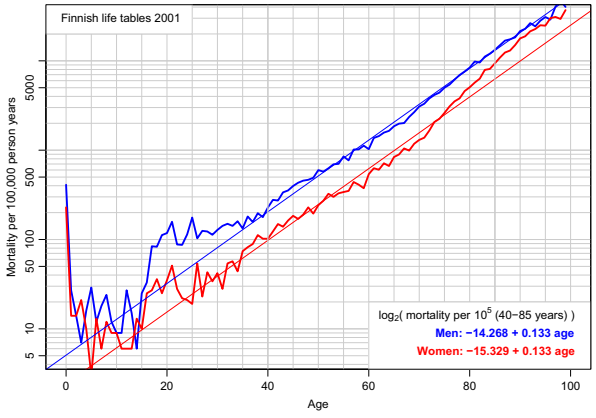

Finnish life tables 1996
Mortality per 100,000 person years
5
10
50
100
500
5000
0
20
40
60
80
100
Age
log2(mortality per 10^5 (40−85 years))
Men: −14.235 + 0.136 age
Women: −15.388 + 0.136 age

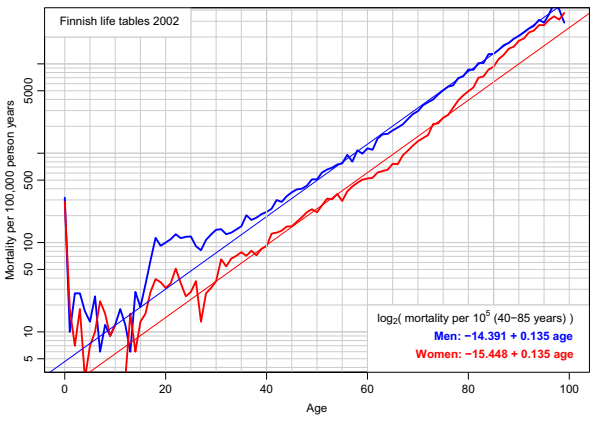

Finnish life tables 1997
Mortality per 100,000 person years
5
10
50
100
500
5000
0
20
40
60
80
100
Age
log2(mortality per 10^5 (40−85 years))
Men: −14.151 + 0.134 age
Women: −15.235 + 0.134 age

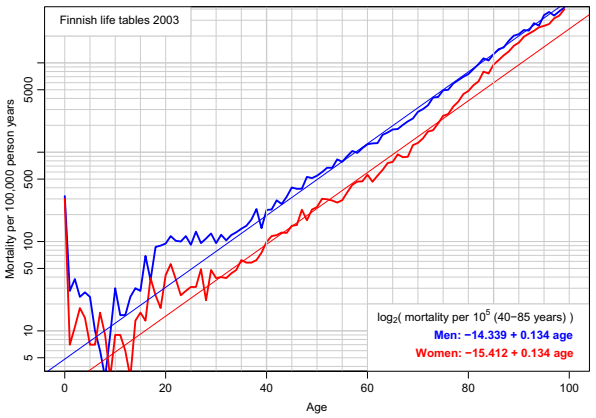












Who needs the Cox-model anyway?

Monday 23rd, afternoon

Bendix Carstensen

Age-Period-Cohort models
March 2009
Max Planck Institut for Demographic Research, Rostock
`www.biostat.ku.dk/~bxc/APC/MPIDR-2009`

Empirical rates

At the individual level we introduce the **empirical rate:** (d, y),
— the number of events ($d \in \{0, 1\}$) during y risk time.

Each individual contributes several observations.

Empirical rates are **responses** in survival analysis.

The timescale is a **covariate** — varies across empirical rates from one individual.

Likelihood

The likelihood from several empirical rates from one individual is a product of conditional probabilities. Hence, the log-likelihood contribution from one individual is a sum of terms.

The log-likelihood from one empirical rate (d, y), assuming the event rate λ is constant is:

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

so the contribution from one individual is as the contribution from several independent Poisson observations.

The proportional hazards 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.
- Conceptually it is less clear — t is but a covariate that varies within individual.

Cox-likelihood

The partial likelihood for the regression parameters:

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

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

Regression parameters describing the effect of covariates (other than the chosen underlying time scale).
One parameter per death time to describe the effect of time (i.e. the chosen timescale).

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

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 $(d, y) = (1, 1)$ from the person that died at time t.
- all other empirical rates $(d, y) = (0, 1)$ 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.

What the Cox-model really is

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

- dividing time as finely as possible,
- modelling one covariate, the time-scale, with one parameter per distinct value,
- profiling these parameters out by maximizing the profile likelihood

Subsequently, one may recover the effect of the timescale by smoothing an estimate of the cumulative sum of these.

Sensible modelling

Replace the α_ts by a parmetric function $f(t)$ with a limited number of parameters, for example:

- Piecewise constant
- Splines (linear, quadratic or cubic)
- Fractional polynomials

Use Poisson modelling software on a dataset of empirical rates for small intervals (ys).

Note that the intervals need not be derived from the death times.

Just small enough to make the constant rate assumption reasonable.

Splitting the dataset

The Poisson approach needs a dataset of empirical rates with small values of y.

Larger than the original: each individual contributes many empirical rates. 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

Example: Mayo Clinic lung cancer

```
  time status age sex
1  306      2  74   1
2  455      2  68   1

> Lx <- Lexis( exit=list( tfd=time), exit.status=(status==2), da
NOTE: entry is assumed to be 0 on the tfd timescale.

> tab(Lx,scale=365.25)
States:
     #records:
     To
From    FALSE TRUE Sum  #events:  #risk time:      Rate      (95
  FALSE    63  165 228       165     190.5352 0.8659815 0.743432

> dx <- splitLexis( Lx, "tfd", breaks=c(0,unique(Lx$time)) )
> tab( dx, scale=365.25 )
States:
     #records:
     To
From    FALSE TRUE   Sum  #events:  #risk time:      Rate      (
  FALSE 19857  165 20022       165     190.5352 0.8659815 0.7434
```


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 $\mathrm{diag}\big[\exp\big(\hat{f}(t_i)\big)\big]$

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

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

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

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

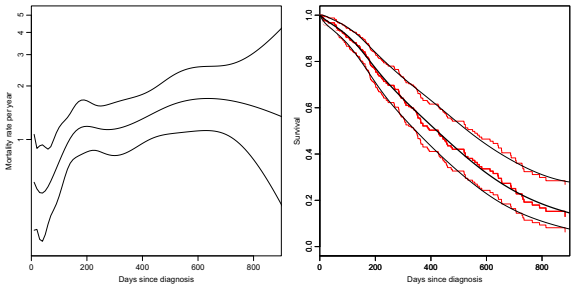
8. Variance-covariance matrix for the cumulative hazard is:

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

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

Mayo clinic lung cancer data

Smoothing by natural splines with 7 parameters; knots at $0, 25, 75, 150, 250, 500, 1000$ days



Computational tools for time-splitting

R: A function `splitLexis`, written by Martyn Plummer, in the package `Epi` available at CRAN.

Stata: The function `stsplit` (part of standard Stata).
Descendant of `stlexis` written by Michael Hills & David Clayton.

SAS: A macro `%Lexis`, available at `http://wwww.biostat.ku.dk/~bxc/Lexis`.

Conclusion

- 1 — 1 correspondence between life-tables and classical survival analysis.
- Cox-model (and the Kaplan-Meier estimator) is the lifetable taken ad absurdum, estimating one probability per interval defined by events/censorings.
- The natural modification is to use the modified life table estimator as basis for Poisson modelling.

Follow-up data
Monday 23rd, afternoon

Bendix Carstensen

Age-Period-Cohort models
March 2009
Max Planck Institut for Demographic Research, Rostock
`www.biostat.ku.dk/~bxc/APC/MPIDR-2009`

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

Age	subj. 1 Y	D	subj. 2 Y	D	subj. 3 Y	D	$\sum$ 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

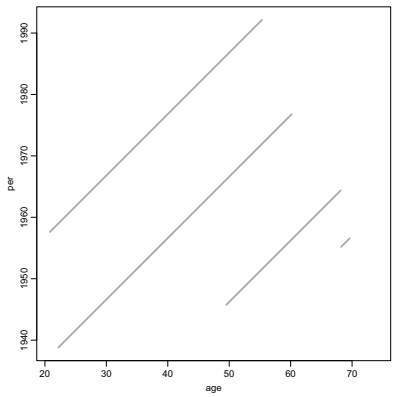
Definition of `Lexis` object

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

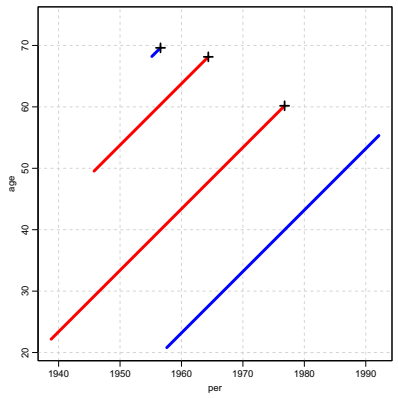
`entry` is defined on **three** timescales,
but `exit` is only defined on **one** timescale:
Follow-up time is the same on all timescales.

The looks of a `Lexis` object

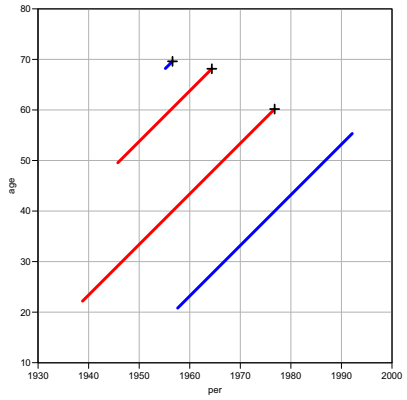
```
> round( thL[,c(1:8,14,15)], 2 )
    age     per tfi lex.dur lex.Cst lex.Xst lex.id   ic
1 22.18 1938.79   0   38.00       0       1      1    1
2 49.55 1945.77   0   18.60       0       1      2  640
3 68.21 1955.18   0    1.40       0       1      3 3425
4 20.80 1957.61   0   34.52       0    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


```
> 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 bi
1      1 22.18 1938.79  0.00   17.82       0       0    1   2  1
2      1 40.00 1956.61 17.82   20.00       0       0    1   2  1
3      1 60.00 1976.61 37.82    0.18       0       1    1   2  1
4      2 49.55 1945.77  0.00   10.45       0       0  640   2  1
5      2 60.00 1956.23 10.45    8.14       0       1  640   2  1
6      3 68.21 1955.18  0.00    1.40       0       1 3425   1  1
7      4 20.80 1957.61  0.00   19.20       0       0 4017   2  1
8      4 40.00 1976.81 19.20   15.33       0       0 4017   2  1
```


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 b
1       1 22.18 1938.79  0.00    1.00       0       0    1   2
2       1 23.18 1939.79  1.00    4.00       0       0    1   2
3       1 27.18 1943.79  5.00   12.82       0       0    1   2
4       1 40.00 1956.61 17.82    2.18       0       0    1   2
5       1 42.18 1958.79 20.00   17.82       0       0    1   2
6       1 60.00 1976.61 37.82    0.18       0       1    1   2
7       2 49.55 1945.77  0.00    1.00       0       0  640   2
8       2 50.55 1946.77  1.00    4.00       0       0  640   2
9       2 54.55 1950.77  5.00    5.45       0       0  640   2
10      2 60.00 1956.23 10.45    8.14       0       1  640   2
11      3 68.21 1955.18  0.00    1.00       0       0 3425   1
12      3 69.21 1956.18  1.00    0.40       0       1 3425   1
13      4 20.80 1957.61  0.00    1.00       0       0 4017   2
14      4 21.80 1958.61  1.00    4.00       0       0 4017   2
15      4 25.80 1962.61  5.00   14.20       0       0 4017   2
```


The Poisson likelihood for time-split data

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

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

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

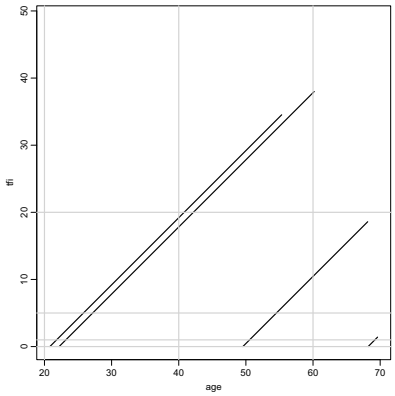
If $d \sim \text{Poisson}(\lambda y)$, i.e. with mean (λy) then the log-likelihood is

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

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 b
1       1 22.18 1938.79  0.00    1.00       0       0    1   2
2       1 23.18 1939.79  1.00    4.00       0       0    1   2
3       1 27.18 1943.79  5.00   12.82       0       0    1   2
4       1 40.00 1956.61 17.82    2.18       0       0    1   2
5       1 42.18 1958.79 20.00   17.82       0       0    1   2
6       1 60.00 1976.61 37.82    0.18       0       1    1   2
7       2 49.55 1945.77  0.00    1.00       0       0  640   2
8       2 50.55 1946.77  1.00    4.00       0       0  640   2
9       2 54.55 1950.77  5.00    5.45       0       0  640   2
10      2 60.00 1956.23 10.45    8.14       0       1  640   2
11      3 68.21 1955.18  0.00    1.00       0       0 3425   1
12      3 69.21 1956.18  1.00    0.40       0       1 3425   1
13      4 20.80 1957.61  0.00    1.00       0       0 4017   2
14      4 21.80 1958.61  1.00    4.00       0       0 4017   2
15      4 25.80 1962.61  5.00   14.20       0       0 4017   2
16      4 40.00 1976.81 19.20    0.80       0       0 4017   2
17      4 40.80 1977.61 20.00   14.52       0       0 4017   2
```

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.

Age at entry
Monday 23rd, afternoon

Bendix Carstensen

Age-Period-Cohort models
March 2009
Max Planck Institut for Demographic Research, Rostock
`www.biostat.ku.dk/~bxc/APC/MPIDR-2009`

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.

Models for tabulated data
Monday 23rd, afternoon

Bendix Carstensen

Age-Period-Cohort models
March 2009
Max Planck Institut for Demographic Research, Rostock
`www.biostat.ku.dk/~bxc/APC/MPIDR-2009`

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.

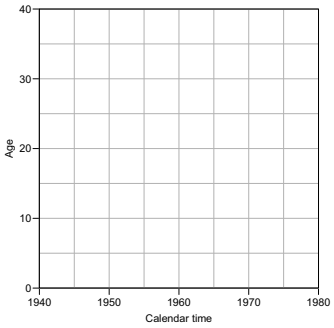
Realistic set-up

- 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]

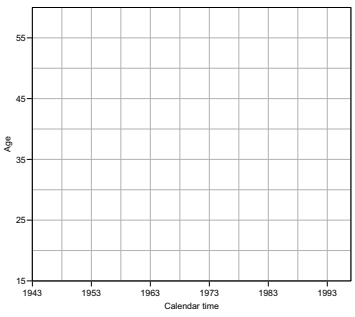


Disease registers record events.

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



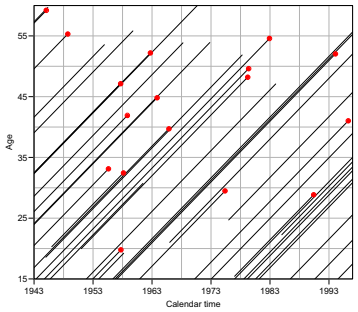
Registration of:

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
2 20 1958  8 770859
3 25 1958 35 698612
```


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
factor(P)1948  0.1753     0.1211   1.447  0.14778
factor(P)1953  0.3822     0.1163   3.286  0.00102
```


`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

Tuesday 24th, morning

Bendix Carstensen

Age-Period-Cohort models
March 2009
Max Planck Institut for Demographic Research, Rostock
`www.biostat.ku.dk/~bxc/APC/MPIDR-2009`

Register data - rates

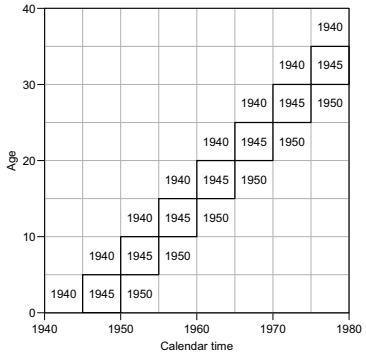
Rates in "tiles" of the Lexis diagram:

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

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).

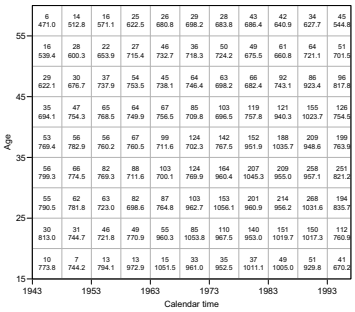
Synthetic cohorts



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
15–19	7	13	13	15	33	35	37	49
20–24	31	46	49	55	85	110	140	151
25–29	62	63	82	87	103	153	201	214
30–34	66	82	88	103	124	164	207	209
35–39	56	56	67	99	124	142	152	188
40–44	47	65	64	67	85	103	119	121
45–49	30	37	54	45	64	63	66	92
50–54	28	22	27	46	36	50	49	61
55–59	14	16	25	26	29	28	43	42

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
15–19	744.2	794.1	972.9	1051.5	961.0	952.5	1011.1	1005.0
20–24	744.7	721.8	770.9	960.3	1053.8	967.5	953.0	1019.7
25–29	781.8	723.0	698.6	764.8	962.7	1056.1	960.9	956.2
30–34	774.5	769.3	711.6	700.1	769.9	960.4	1045.3	955.0
35–39	782.9	760.2	760.5	711.6	702.3	767.5	951.9	1035.7
40–44	754.3	768.5	749.9	756.5	709.8	696.5	757.8	940.3
45–49	676.7	737.9	753.5	738.1	746.4	698.2	682.4	743.1
50–54	600.3	653.9	715.4	732.7	718.3	724.2	675.5	660.8
55–59	512.8	571.1	622.5	680.8	698.2	683.8	686.4	640.9

Data matrix: Empirical rates

Rate per 1000,000 person-years

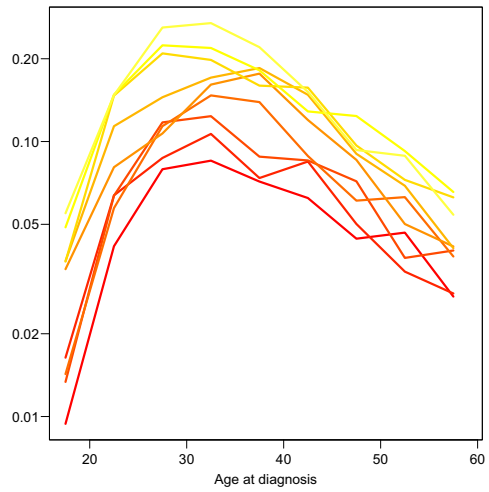
	Date of diagnosis $(year - 1900)$							
Age	48–52	53–57	58–62	63–67	68–72	73–77	78–82	83–87
15–19	9.4	16.4	13.4	14.3	34.3	36.7	36.6	48.8
20–24	41.6	63.7	63.6	57.3	80.7	113.7	146.9	148.1
25–29	79.3	87.1	117.4	113.8	107.0	144.9	209.2	223.8
30–34	85.2	106.6	123.7	147.1	161.1	170.8	198.0	218.8
35–39	71.5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

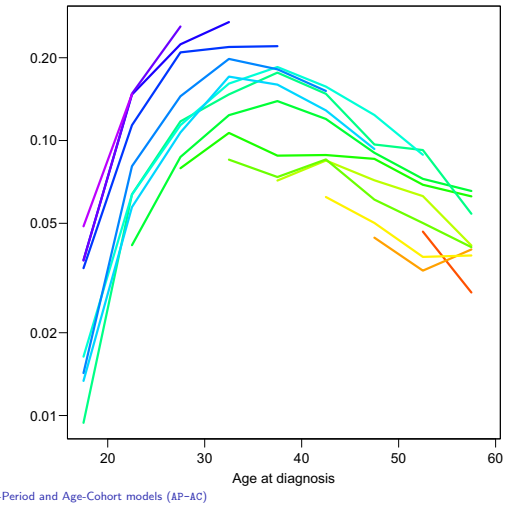
The classical plots

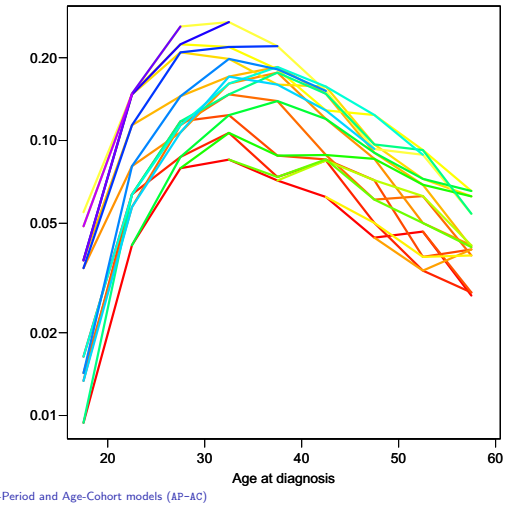
Given a table of rates classified by age and period, we can do 4 "classical" plots:

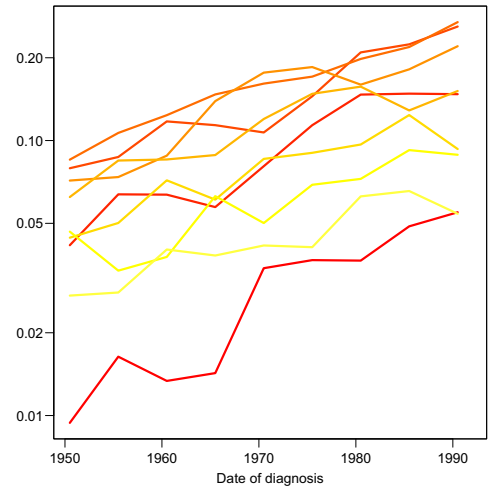
- Rates versus age at diagnosis (period):
  — rates in the same ageclass connected.
- Rates versus age at diagnosis:
  — rates in the same birth-cohort connected.
- Rates versus date of diagnosis:
  — rates in the same ageclass connected.
- Rates versus date of date of birth:
  — rates in the same ageclass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

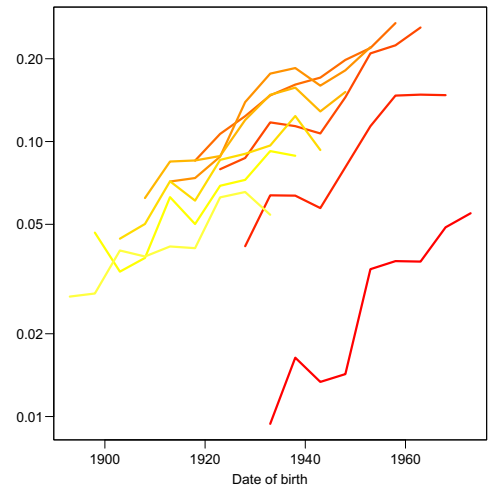
These plots can be produced by the R-function `rateplot`.











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 $\beta_{p_0} = 0$

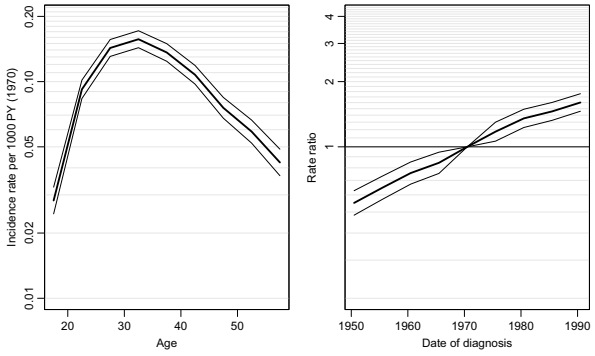
$$\log[\lambda(a,p_0)] = \alpha_a + \beta_{p_0} = \alpha_a$$

Fitting the model in R

Reference period is the 5th period (1970.5 ∼ 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

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 $\gamma_{c_0} = 0$

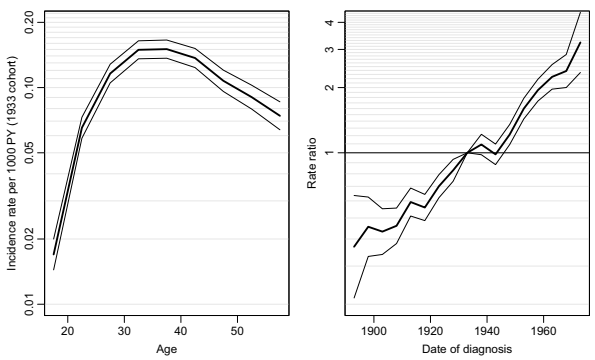
$$\log[\lambda(a,c_0)] = \alpha_a + \gamma_{c_0} = \alpha_a$$

Fit the model in R

Reference period is the 9th cohort (1933 ∼ 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

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
Tuesday 24th, morning

Bendix Carstensen

Age-Period-Cohort models
March 2009
Max Planck Institut for Demographic Research, Rostock
www.biostat.ku.dk/~bxc/APC/MPIDR-2009

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))

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:

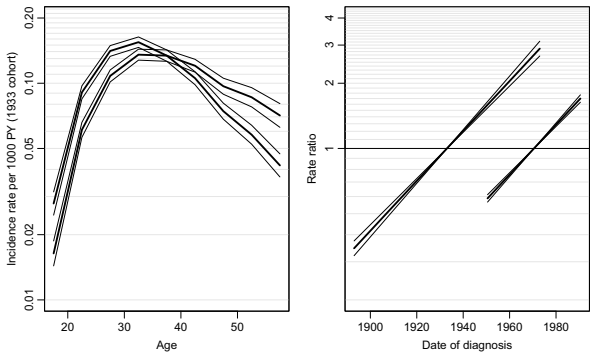
```
> acd <- glm( D ~ factor( A ) - 1 + I(C-1933) +
+             offset( log( Y ) ),
+             family=poisson )
> summary( acd )

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

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?

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

The two models are the same.
The **parametrization** is different.

The age-curve refers either
- to a period (cross-sectional rates) or
- to a cohort (longitudinal rates).



Which age-curve is period and which is cohort?

Age-Period-Cohort model
Tuesday 24th, afternoon

Bendix Carstensen

Age-Period-Cohort models
March 2009
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www.biostat.ku.dk/~bxc/APC/MPIDR-2009

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.

Fitting the model in R

```
> c1933.p <- glm( D ~ factor( A ) - 1 +
+                     relevel( factor( C ), "1933" ) +
+                     factor( P ) + offset( log( Y ) ), family=p
> summary( c1933.p )
Coefficients: (1 not defined because of singularities)
                              Estimate Std. Error z value Pr(>|
factor(A)17.5                 -4.27754    0.10479 -40.819  < 2e
...
factor(A)57.5                 -2.75892    0.08380 -32.922  < 2e
relevel(factor(C), "1933")1893 -0.84187    0.28009  -3.006  0.00
...
relevel(factor(C), "1933")1928 -0.17922    0.05965  -3.005  0.00
relevel(factor(C), "1933")1938  0.07540    0.05592   1.348  0.17
...
relevel(factor(C), "1933")1973  1.37438    0.17490   7.858 3.90e
factor(P)1955.5                 0.04793    0.07022   0.683  0.49
...
factor(P)1985.5                 0.09276    0.04091   2.267  0.02
factor(P)1990.5                      NA         NA      NA

(Dispersion parameter for poisson family taken to be 1)
    Null deviance: 89358.526  on 81  degrees of freedom
Residual deviance:    35.459  on 49  degrees of freedom
```

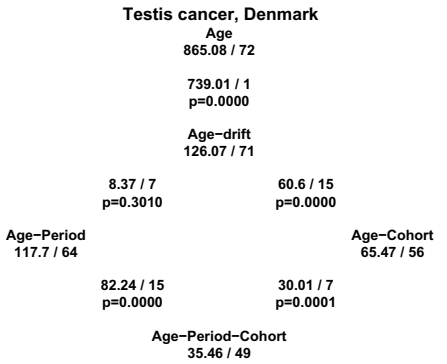

No. of parameters

A has 9 levels
P has 9 levels
C 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

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

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 programs: Put extremes of periods or cohorts to 0, and choose a reference for the other.

Holford: Extract linear effects by regression:

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

$$\begin{aligned}&= \tilde{\alpha}_a + \hat{\mu}_a + \hat{\delta}_a a + \\ &\quad \tilde{\beta}_p + \hat{\mu}_p + \hat{\delta}_p p + \\ &\quad \tilde{\gamma}_c + \hat{\mu}_c + \hat{\delta}_c c\end{aligned}$$

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:

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

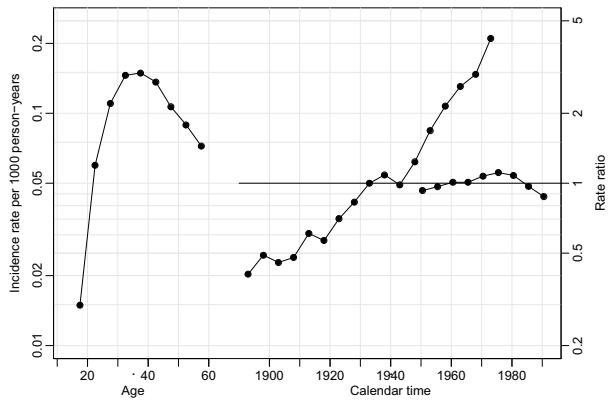
The rest is the age-effect:

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

How it 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 $\hat{\gamma}_c$:

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

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

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

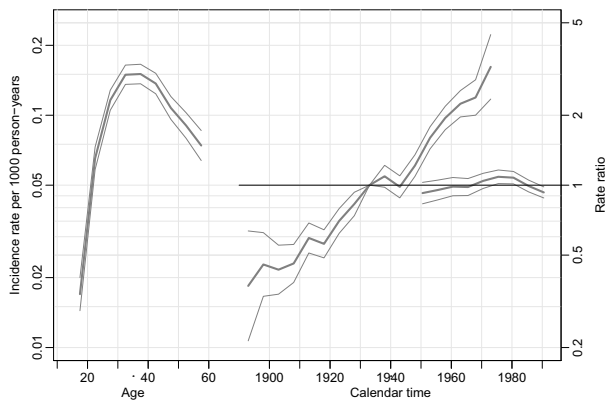
The residual period effect can be estimated if we note that for the number of cases we have:

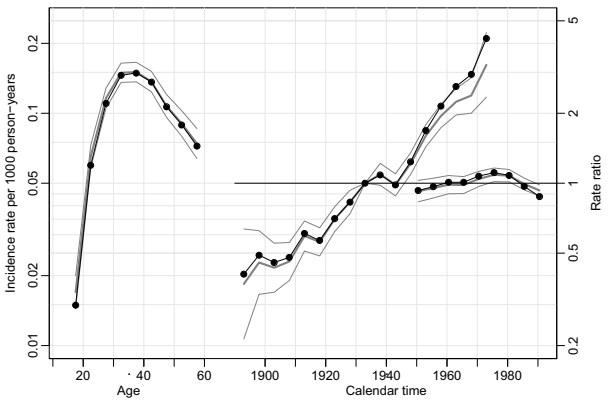
$$\log(\text{expected cases}) = \log[\lambda(a,p)Y] = \underbrace{\hat{\alpha}_a + \hat{\gamma}_c + \log(Y)}_{\text{"known"}} + \beta_p$$

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..





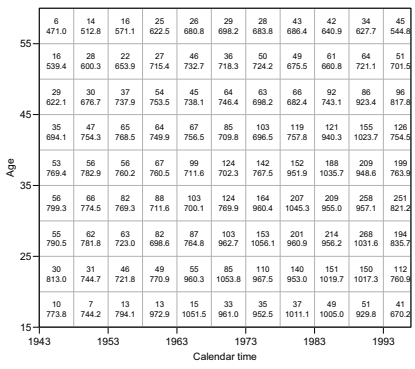
Tabulation in the Lexis diagram

Tuesday 24th, morning

Bendix Carstensen

Age-Period-Cohort models
March 2009
Max Planck Institut for Demographic Research, Rostock
`www.biostat.ku.dk/~bxc/APC/MPIDR-2009`

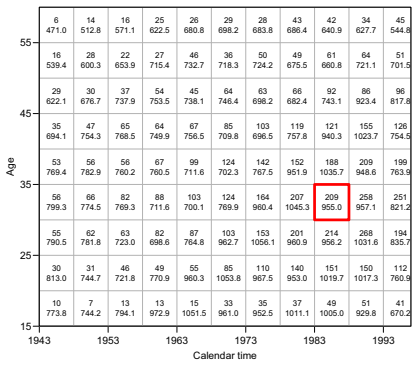
Tabulation of register data



Testis cancer cases in Denmark.

Male person-years in Denmark.

Tabulation of register data



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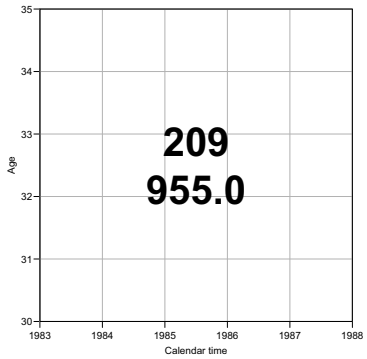

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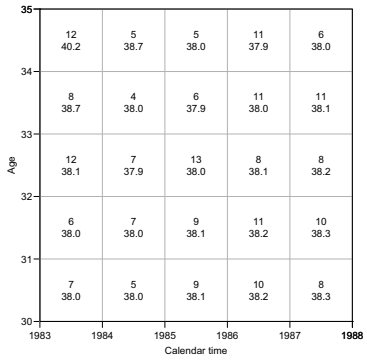
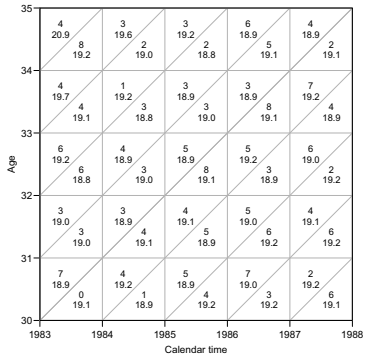
Tabulation of register data



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. (◸)

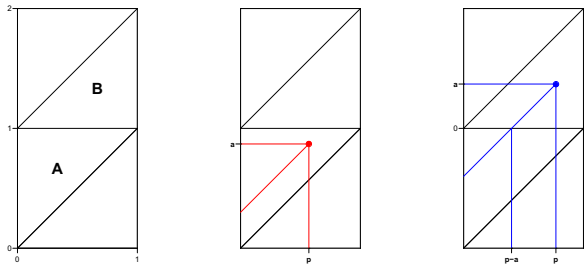
Lower triangles: Classification by age and cohort, last born cohort. (◿)

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:

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

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

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

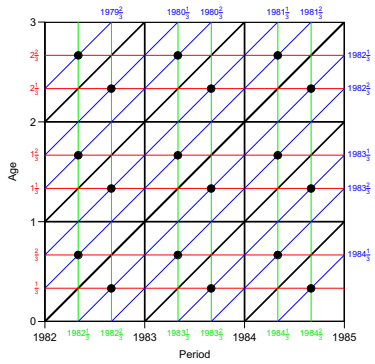
Lower triangles (◿), B:

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

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

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

Tabulation by age, period and cohort



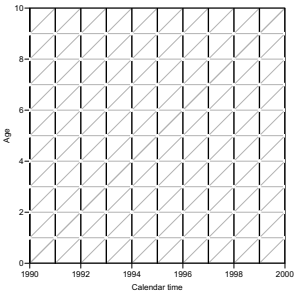
Gives triangular sets with differing mean age, period and cohort:

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 bureaux.

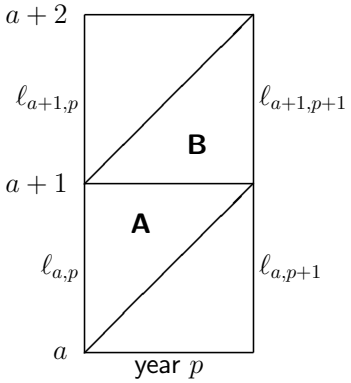
This corresponds to population sizes along the vertical lines indicated in the diagram. We want risk time figures for the population in the squares and triangles in the diagram.



Prevalent population figures

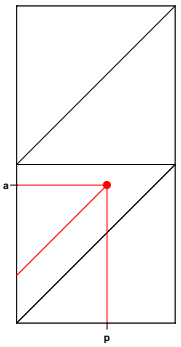
$\ell_{a,p}$ is the number of persons in age calss a alive at the beginning of period (=year) p.

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



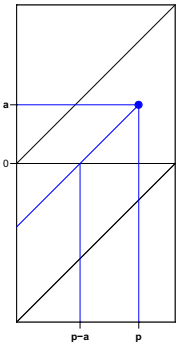
A person dying in age a at date p in **A** contributes p risk time, so the average will be:

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



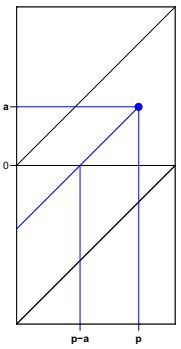
A person dying in age a at date p in **B** contributes $p-a$ risk time in **A**, so the average will be:

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



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

$$\int_{p=0}^{p=1}\int_{a=0}^{a=p} 2a \; \mathrm{d}a \; \mathrm{d}p = \int_{p=0}^{p=1} p^2 \; \mathrm{d}p = \frac{1}{3}$$



Contributions to risk time in A and B:

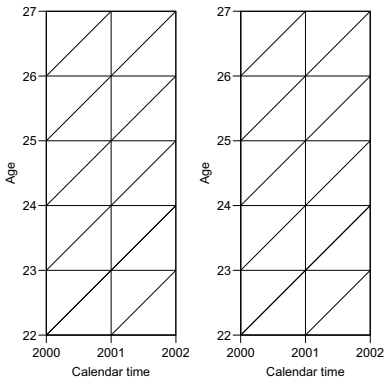
	A:	**B**:
Survivors:	$\ell_{a+1,p+1} \times \frac{1}{2}$y	$\ell_{a+1,p+1} \times \frac{1}{2}$y
Dead in **A**:	$\frac{1}{2}(\ell_{a,p} - \ell_{a+1,p+1}) \times \frac{1}{3}$y	
Dead in **B**:	$\frac{1}{2}(\ell_{a,p} - \ell_{a+1,p+1}) \times \frac{1}{3}$y	$\frac{1}{2}(\ell_{a,p} - \ell_{a+1,p+1}) \times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



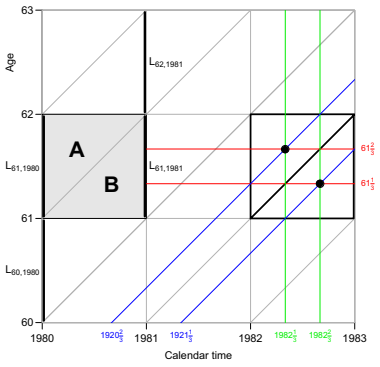
Summary:

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

Wednesday 25th, morning

Bendix Carstensen

Age-Period-Cohort models
March 2009
Max Planck Institut for Demographic Research, Rostock
`www.biostat.ku.dk/~bxc/APC/MPIDR-2009`

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:

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

The log-likelihood can be separated:

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

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

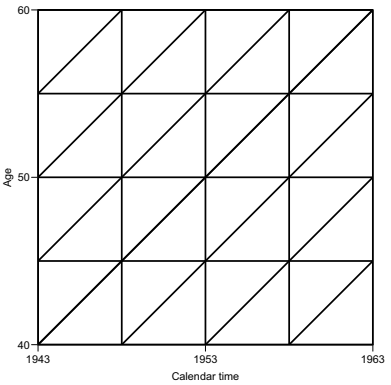
Illustration by lung cancer data

```
> 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.

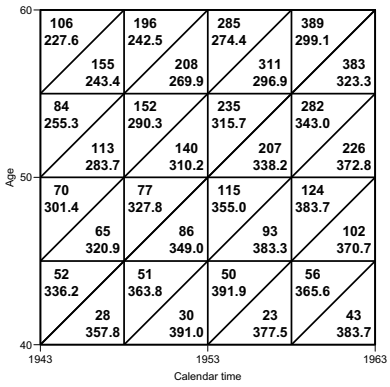
Mark mean date of birth for these.

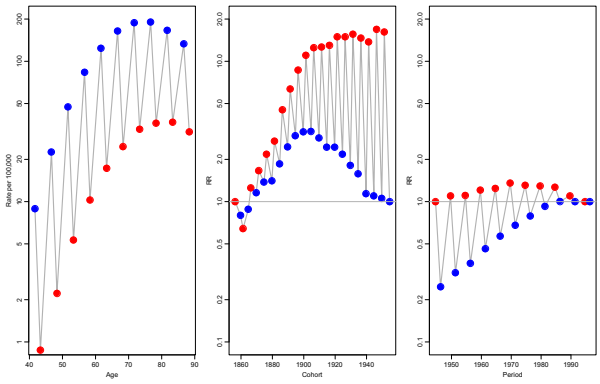


Fill in the number of cases (D) and person-years (Y) from previous slide.

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

Mark mean date of birth for these.





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: $220 - 182 = 38$.

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

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

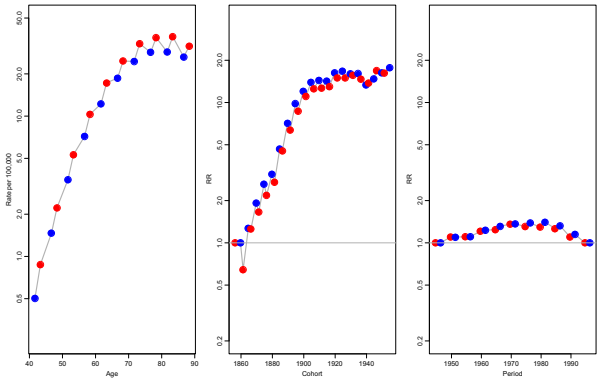

APC-model with "correct" cohorts

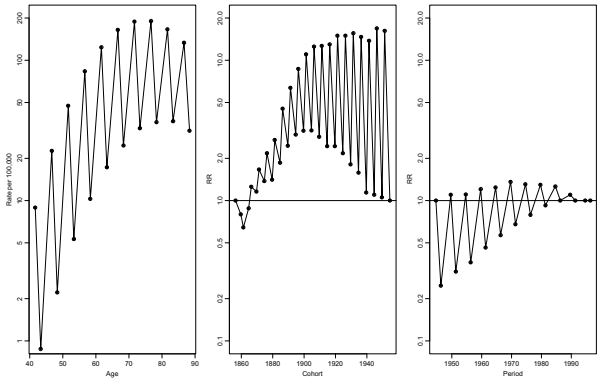
```
> mx <- glm( D ~ factor(Ax) - 1 +
+                factor(Cx) +
+                factor(Px) + offset( log( Y ) ),
+            family=poisson )
> summary( mx )
...
    Null deviance: 1.0037e+08  on 220  degrees of freedom
Residual deviance: 2.8473e+02  on 144  degrees of freedom
```

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

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

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





APC-model: Parametrization

Wednesday 25th, afternoon

Bendix Carstensen

Age-Period-Cohort models
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What's the problem?

One parameter is assigned to each distinct value of the timescales, the ordering of the variables is not used.

The solution is to "tie together" the points on the scales together with smooth functions of the *mean* age, period and cohort with three functions:

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

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

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

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

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:

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

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?

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?

Implementation:

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

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

3. Use the functions:

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

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(M)` is the number of observations in the dataset.

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$([1|p])$.

(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 $[1|c]$.
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), log-rate θ:

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

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

Two relevant inner products:

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

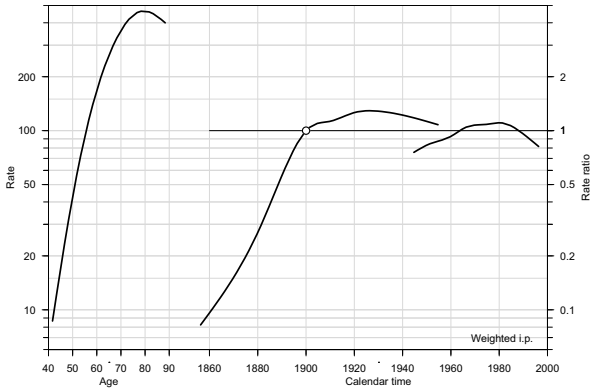
the weights could be chosen as $w_i = D_i$, i.e. proportional to the information content in the units of the dataset.

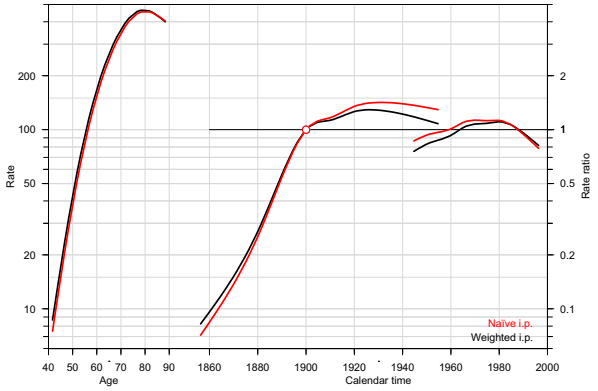
How to?

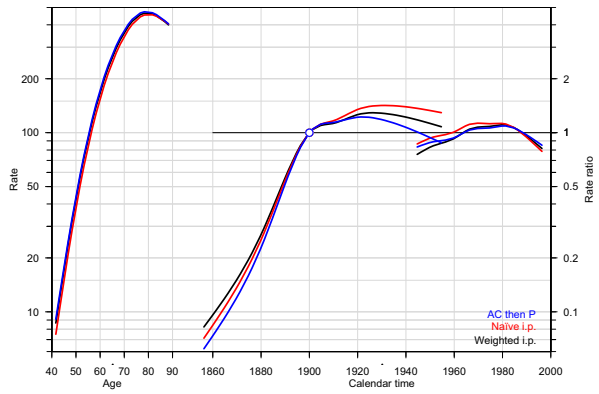
Implemented in `apc.fit`:

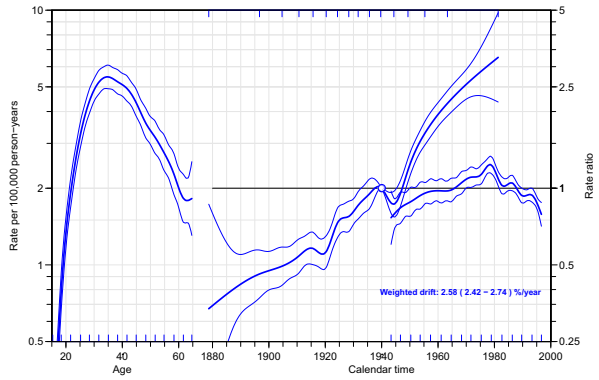
```
m1 <- apc.fit( A=lungDK$Ax,
               P=lungDK$Px,
               D=lungDK$D,
               Y=lungDK$Y/10^5,
           ref.c=1900 )
apc.plot( m1 )
```

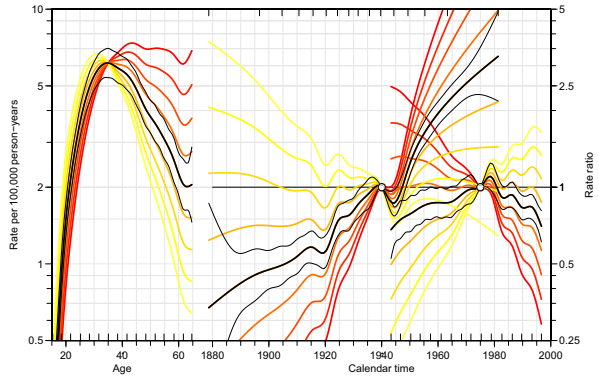
Consult the help page for:
`apc.fit` to see options for weights in inner product, type of function, variants of parametrization etc.
`apc.plot`, `apc.lines` and `apc.frame` to see how to plot the results.











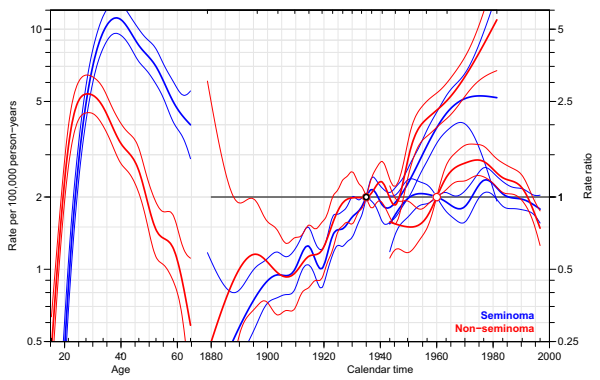
Two sets of data

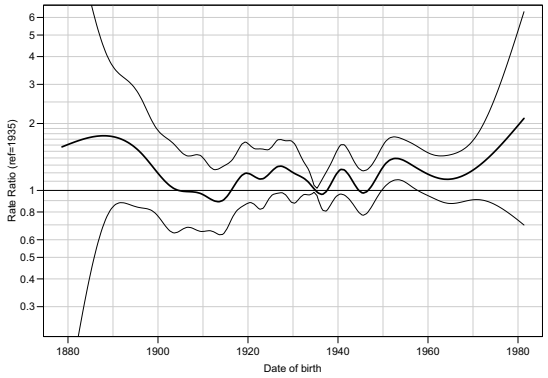
Example: Testis cancer in Denmark, Seminoma and non-Seminoma cases.

```
> stat.table( list( Histology=hist ),
+             list( D=sum(d), Y=sum(y/10^6) ),
+             margins = TRUE )
 ----------------------------
 Histology         D       Y
 ----------------------------
 1           4708.00  127.53
 2           3632.00  127.53
 3            466.00  127.53

 Total       8806.00  382.58
 ----------------------------
```

First step is separate analyses for each subtype.





APC-models for several datasets

Wednesday 25th, afternoon

Bendix Carstensen

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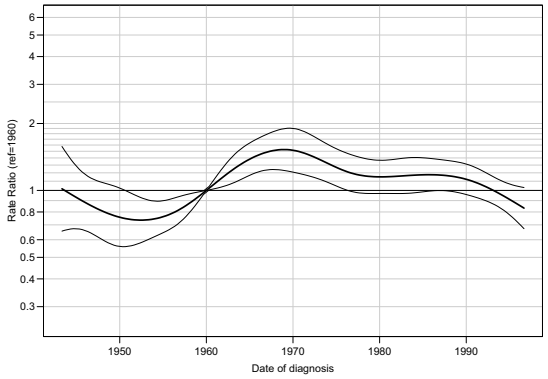


Analysis of two rates: Formal tests I

```
> 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( l
> 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
Model 5: D ~ Mc + Mp + Ma:type + offset(log(Y)) - 1
  Resid. Df Resid. Dev    Df Deviance P(>|Chi|)
```


Analysis of two rates: Formal tests II

```
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

Friday 27th, morning

Bendix Carstensen

Age-Period-Cohort models
March 2009
Max Planck Institut for Demographic Research, Rostock
www.biostat.ku.dk/~bxc/APC/MPIDR-2009

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.Rdat
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

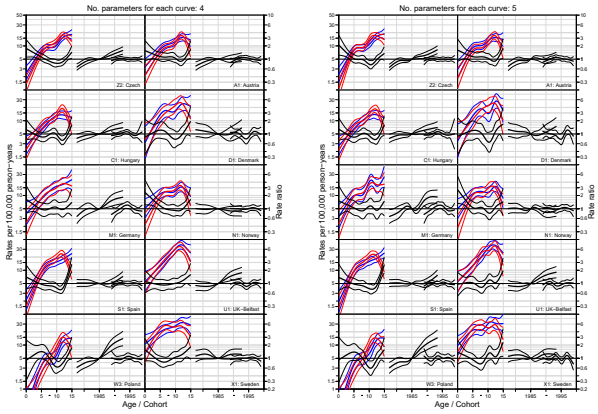
```
P.kn <- quantile( rep( P, D ), probs=pP[-c(1,n.P)] )
P.ok <- quantile( rep( P, D ), probs=pP[ c(1,n.P)] )
P.pt <- sort( P[match( unique(P), P )] )

# 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
Mp <-              detrend( ns( P, kn=P.kn, Bo=P.ok ), P, weight
# 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 )
```

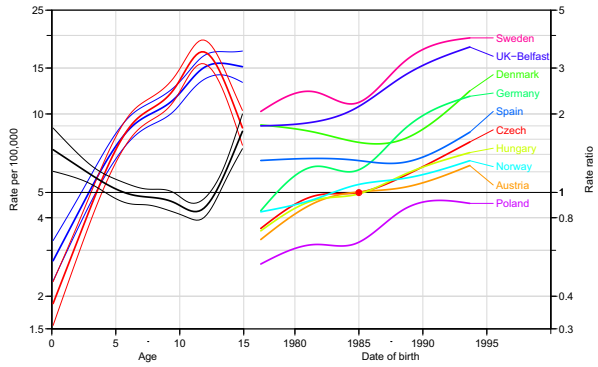

Analysis of DM-rates: Age×sex interaction IV

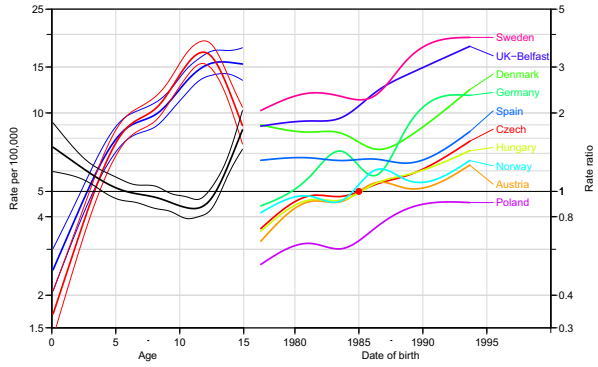
```
ci.lin( apcs )
ci.lin( apcs, subset="sexF", Exp=T)
ci.lin( apcs, subset="sexF", ctr.mat=Pa, Exp=T)

# 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
 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
Friday 27th, morning

Bendix Carstensen

Age-Period-Cohort models
March 2009
Max Planck Institut for Demographic Research, Rostock
`www.biostat.ku.dk/~bxc/APC/MPIDR-2009`

Prediction of future rates

Model:

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

- Why not just extend the estimated functions into the future?
- The parametrization curse — the model as stated is not uniquely parametrized.
- Prediction 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 version:

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

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

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

If this is met, the predictions made will not depend on the parametrizatioin chosen.

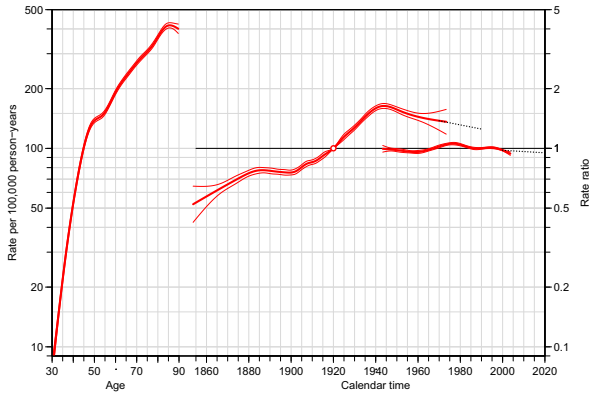
If one of the conditions does not hold, the prediction wil depend on the parametrization chosen.

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.

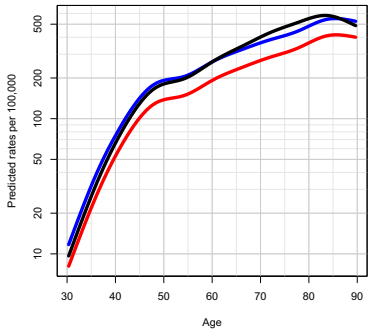
Example: Breast cancer in Denmark



Practicalities

- Long term predicitons notoriously unstable.
- Decreasing slopes are possible, the requitrement 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).