# Representation of follow-up

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# Representation of follow-up

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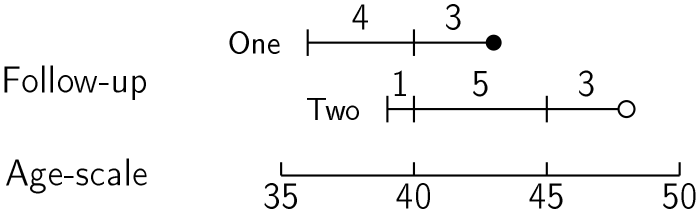
- In follow-up studies we estimate rates from:
    - $D$ — events, deaths
    - $Y$ — person-years
    - $\hat{\lambda} = D/Y$ rates
    - …empirical counterpart of intensity — an **estimate**
- Rates differ between persons.
- Rates differ within persons:
    - by age
    - by calendar time
    - by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

# Stratification by age

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

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

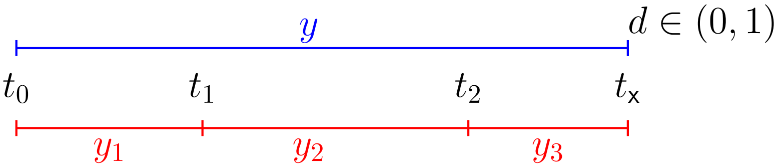


— allowing rates to vary across age-bands

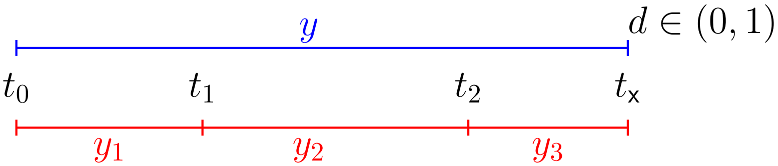
— how do we split follow-up by age and why is it OK?

# Statistical model for follow-up data

- **Data**:
  - status and time at entry
  - status and time at exit
  - . . . **observed** risk time and events (= change of status): **empirical** occurrence rates $(d, y)$
- **Model** for occurrence rates:
  - $\lambda(t, x) = \mathrm{P}\left\{\text{event in } (t, t + \mathrm{d}t] \middle| \text{ alive at } t, \text{x}\right\} / \mathrm{d}t$
  - parametric specification of how $\lambda$ depends on $t$ and $x$
  - likelihood is a function of $\lambda$ and **data**: $\mathrm{P}\left\{\text{data} \mid \text{model}, \lambda\right\}$
  - simplest case with constant $\lambda$: log-likelihood $= d\log(\lambda) - \lambda y$
  - log-likelihood for a Poisson variate $d$ with expectation $\lambda y$ is: $d\log(\lambda) - \lambda y$, the same as the rate log-likelihood
  - rate model is not a Poisson **model**, but the **likelihood** is the same



| Probability | log-Lik ($\lambda$ constant) |
|---|---|
| $\mathrm{P}(d \text{ at } t_\mathsf{x} \mid \text{entry } t_0)$ | $d \log(\lambda) - \lambda y$ |
| $= \mathrm{P}(\text{surv } t_0 \rightarrow t_1 \mid \text{entry } t_0)$ | $= 0 \log(\lambda) - \lambda y_1$ |
| $\times \mathrm{P}(\text{surv } t_1 \rightarrow t_2 \mid \text{entry } t_1)$ | $+ 0 \log(\lambda) - \lambda y_2$ |
| $\times \mathrm{P}(d \text{ at } t_\mathsf{x} \mid \text{entry } t_2)$ | $+ d \log(\lambda) - \lambda y_3$ |



| Probability | log-Lik ($\lambda$ varies) |
|---|---|
| $\mathrm{P}(d \text{ at } t_\mathsf{x} \vert \text{entry } t_0)$ | |
| $= \mathrm{P}(\text{surv } t_0 \rightarrow t_1 \vert \text{entry } t_0)$ | $= 0 \log(\lambda_1) - \lambda_1 y_1$ |
| $\times \mathrm{P}(\text{surv } t_1 \rightarrow t_2 \vert \text{entry } t_1)$ | $+ 0 \log(\lambda_2) - \lambda_2 y_2$ |
| $\times \mathrm{P}(d \text{ at } t_\mathsf{x} \vert \text{entry } t_2)$ | $+ d \log(\lambda_3) - \lambda_3 y_3$ |

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

# Dividing time into bands requires:

**Origin:** The date where the time scale is 0:

- Age — 0 at date of birth
- Disease duration — 0 at date of diagnosis
- Occupation exposure — 0 at date of hire

**Intervals:** How should it be subdivided:

- 1-year classes? 5-year classes?
- Equal length?

**Aim:** Separate rate in each interval, mimicking continuous time by using small intervals:
—time at the beginning of interval as quantitative variable.

# Follow-up intervals on several timescales

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

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

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

# Follow-up data in Epi — Lexis objects I

```
> thoro[1:4,1:8]
  id sex birthdat contrast injecdat volume  exitdat exitstat
1  1   2 1916.609        1 1938.791     22 1976.787        1
2  2   2 1927.843        1 1943.906     80 1966.030        1
3  3   1 1902.778        1 1935.629     10 1959.719        1
4  4   1 1918.359        1 1936.396     10 1977.307        1

> thL <- Lexis(entry = list(age = injecdat-birthdat,
+                           dat = injecdat,
+                           tfi = 0),
+                exit = list(dat = exitdat),
+         exit.status = factor(exitstat == 1,
+                              labels = c("Alive","Dead")),
+                data = thoro)
NOTE: entry.status has been set to "Alive" for all.
NOTE: Dropping  2  rows with duration of follow up < tol
```

# Follow-up data in Epi — Lexis objects II

```
> summary(thL, timeScales = TRUE)

Transitions:
     To
From    Alive Dead  Records:  Events: Risk time:  Persons:
  Alive   504 1964      2468     1964   51934.08      2468

Timescales:
age dat tfi
 ""  ""  ""
```

# Definition of Lexis object

```
thL <- Lexis(entry = list(age = injecdat-birthdat,
                          dat = injecdat,
                          tfi = 0),
              exit = list(dat = exitdat),
       exit.status = factor(exitstat == 1,
                            labels = c("Alive","Dead")),
              data = thoro)
```

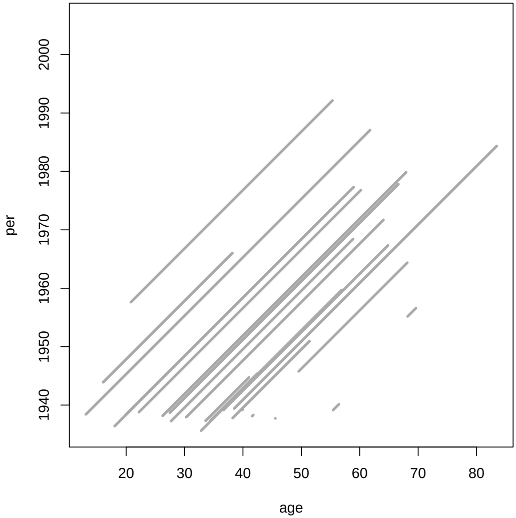
entry is defined on **three** timescales,
but exit is only needed on **one** timescale (or vice versa):
Follow-up time is the same on all timescales: exitdat - injecdat

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

# The looks of a Lexis object

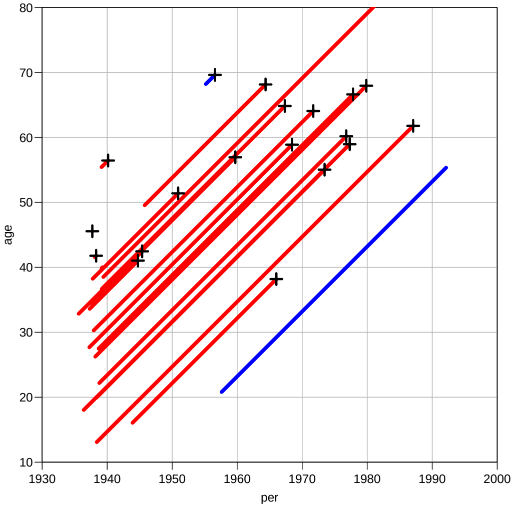
```
> thL[1:4,1:9]
    age     dat tfi lex.dur lex.Cst lex.Xst lex.id
1 22.18 1938.79   0   37.99   Alive    Dead      1
2 49.54 1945.77   0   18.59   Alive    Dead      2
3 68.20 1955.18   0    1.40   Alive    Dead      3
4 20.80 1957.61   0   34.52   Alive   Alive      4
...

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

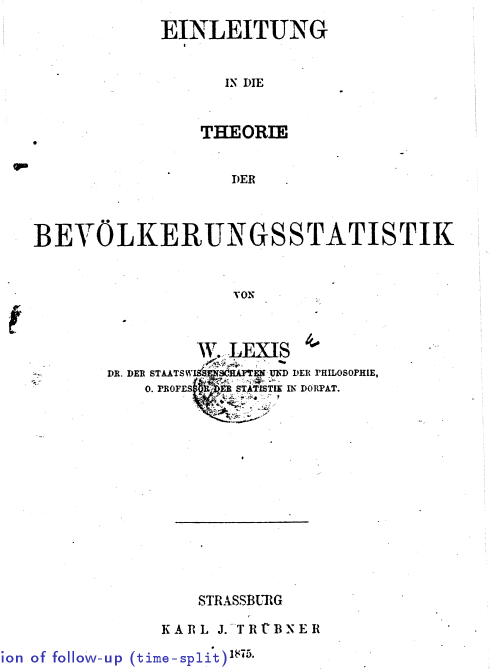


```
> plot( thL, lwd=3 )
```

# Lexis diagram



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



EINLEITUNG

IN DIE

THEORIE

DER

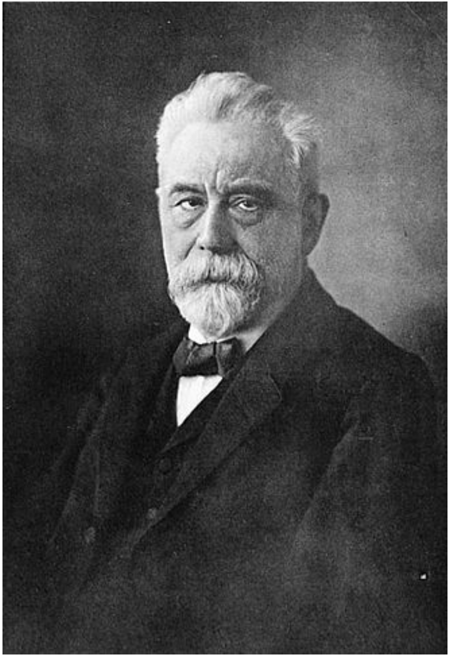
BEVÖLKERUNGSSTATISTIK

VON

W. LEXIS

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

STRASSBURG
KARL J. TRÜBNER
1875.

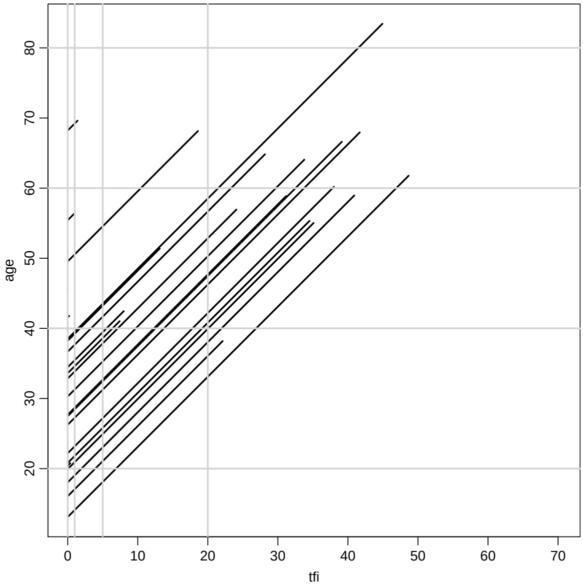


# Splitting follow-up time

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

# Split on another timescale

```
> spl2 <- splitLexis( spl1, time.scale="tfi", breaks=c(0,1,5,20,100) )
> round( spl2, 1 )
   lex.id  age    dat  tfi lex.dur lex.Cst lex.Xst   id sex birthdat contrast inje
1       1 22.2 1938.8  0.0     1.0       0       0    1   2   1916.6        1 19
2       1 23.2 1939.8  1.0     4.0       0       0    1   2   1916.6        1 19
3       1 27.2 1943.8  5.0    12.8       0       0    1   2   1916.6        1 19
4       1 40.0 1956.6 17.8     2.2       0       0    1   2   1916.6        1 19
5       1 42.2 1958.8 20.0    17.8       0       0    1   2   1916.6        1 19
6       1 60.0 1976.6 37.8     0.2       0       1    1   2   1916.6        1 19
7       2 49.5 1945.8  0.0     1.0       0       0  640   2   1896.2        1 19
8       2 50.5 1946.8  1.0     4.0       0       0  640   2   1896.2        1 19
9       2 54.5 1950.8  5.0     5.5       0       0  640   2   1896.2        1 19
10      2 60.0 1956.2 10.5     8.1       0       1  640   2   1896.2        1 19
11      3 68.2 1955.2  0.0     1.0       0       0 3425   1   1887.0        2 19
12      3 69.2 1956.2  1.0     0.4       0       1 3425   1   1887.0        2 19
13      4 20.8 1957.6  0.0     1.0       0       0 4017   2   1936.8        2 19
14      4 21.8 1958.6  1.0     4.0       0       0 4017   2   1936.8        2 19
15      4 25.8 1962.6  5.0    14.2       0       0 4017   2   1936.8        2 19
16      4 40.0 1976.8 19.2     0.8       0       0 4017   2   1936.8        2 19
17      4 40.8 1977.6 20.0    14.5       0       0 4017   2   1936.8        2 19
```



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

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

# Splitting on several timescales

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

Transitions:
     To
From    Alive Dead  Records:  Events: Risk time:  Persons:
  Alive  8250 1964     10214     1964   51934.08      2468

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

Transitions:
     To
From    Alive Dead  Records:  Events: Risk time:  Persons:
  Alive  8248 1964     10212     1964   51916.98      2468

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

# Likelihood for time-split data

- We assume that rates are constant in each (small) interval
- Each observation in the dataset represents an interval, contributing a term to the (log-)likelihood for the rate
- Each **term** looks like a contribution from a Poisson variate (albeit with values only $0$ or $1$)
- So the likelihood from a single **person** looks like the likelihood from several independent Poisson variates
- . . . but the data are neither independent nor Poisson

# Analysis of time-split data

Observations (records) classified by $p$—person and $i$—interval

- $d_{pi}$ — events in the variable: `lex.Xst & lex.Xst!=lex.Cst`
- $y_{pi}$ — risk time: `lex.dur` (duration)
- Covariates are:
  - timescales (age, period, time since entry)
  - other variables for this person (constant in each interval).
- Likelihood for rates for one person is identical to a Poisson likelihood for many independent Poisson variates
- Modeling rates using `glm` or `gam`: time-scales and other covariates are treated alike

# Fitting a simple model—data:

```
> stat.table(contrast,
+            list(D = sum(lex.Xst == "Dead"),
+                 Y = sum(lex.dur),
+              Rate = ratio(lex.Xst == "Dead", lex.dur, 100)),
+            margin = TRUE,
+              data = spl2)
 ------------------------------------
 contrast         D         Y    Rate
 ------------------------------------
 1           928.00 20094.74    4.62
 2          1036.00 31839.35    3.25

 Total      1964.00 51934.08    3.78
 ------------------------------------
```

# Fitting a simple model with poisson

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

```
> m0 <- glm((lex.Xst == "Dead") ~ factor(contrast) - 1,
+           offset = log(lex.dur / 100),
+           family = poisson,
+             data = spl2)
> round(ci.exp(m0), 2)
                  exp(Est.) 2.5% 97.5%
factor(contrast)1      4.62 4.33  4.93
factor(contrast)2      3.25 3.06  3.46
```

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

# Fitting a simple model with poisreg

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

```
> m0 <- glm(cbind(lex.Xst == "Dead", lex.dur / 100) ~ factor(contrast) - 1,
+           family = poisreg,
+             data = spl2)
> round(ci.exp(m0), 2)
                  exp(Est.) 2.5% 97.5%
factor(contrast)1      4.62 4.33  4.93
factor(contrast)2      3.25 3.06  3.46
```

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

# Fitting a simaple model with glm.Lexis

The wrapper glm.Lexis requires that lex.Cst and lex.Xst are factors — see factorize:

```
> m0 <- glm.Lexis(spl2, ~ factor(contrast) - 1, scale = 100)

stats::glm Poisson analysis of Lexis object spl2 with log link:
Rates for the transition:
Alive->Dead
, lex.dur (person-time) scaled by 100

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

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

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

# Fitting a simple model — aggregate data

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

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

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

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

# SMR

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June 2024

# Cohorts where all are exposed

When there is no comparison group we may ask:
Do mortality rates in cohort differ from those of an **external** population, for example:

Rates from:

- Occupational cohorts
- Patient cohorts

compared with reference rates obtained from:

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

# Cohort rates vs. population rates: RSR

- **Additive:** $\lambda(a) = \delta(a) + \lambda_{\mathsf{p}}(a)$,  $\lambda_{\mathsf{p}}$ assumed known
- Note that the survival (since $a = a_0$, say) is:

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

- **Additive** model for **rates** ⇔ **Relative survival** model.

# Cohort rates vs. population rates: SMR

- **Multiplicative:** $\lambda(a) = \theta \times \lambda_{\mathsf{p}}(a)$
- Cohort rates proportional to reference rates, $\lambda_{\mathsf{p}}$:
  $\lambda(a) = \theta \times \lambda_{\mathsf{p}}(a)$ — $\theta$ the same in all age-bands.
- $D_a$ deaths during $Y_a$ person-years an age-band $a$ gives the likelihood:

$$\begin{aligned} D_a \log(\lambda(a)) - \lambda(a) Y_a &= D_a \log(\theta \lambda_{\mathsf{p}}(a)) - \theta \lambda_{\mathsf{p}}(a) Y_a \\ &= D_a \log(\theta) + D_a \log(\lambda_{\mathsf{p}}(a)) - \theta(\lambda_{\mathsf{p}}(a) Y_a) \end{aligned}$$

- The constant $D_a \log(\lambda_{\mathsf{p}}(a))$ does not involve $\theta$, and so can be dropped.

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

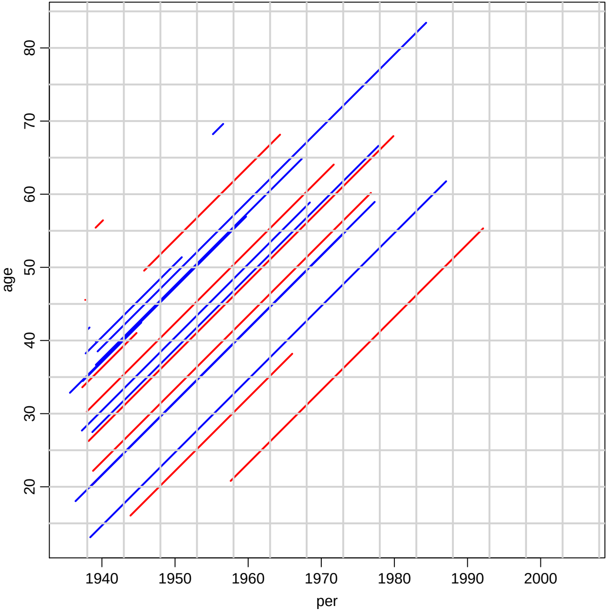
$$D_a \log(\theta) - \theta\big(\lambda_{\mathsf{p}}(a)Y_a\big) = D_a \log(\theta) - \theta(E_a)$$

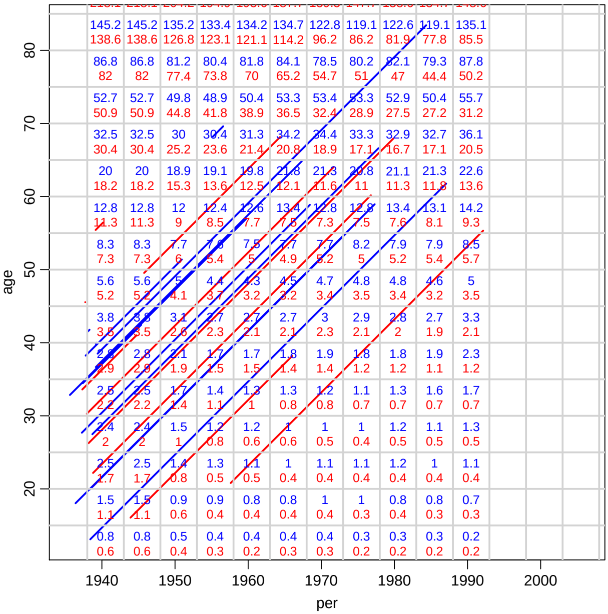
- The log-likelihood is similar to the log-likelihood for a rate, just with $Y$ replaced by $E$, so:

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

# Modeling the SMR in practice

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


80
70
60
50
40
30
20
age
1940
1950
1960
1970
1980
1990
2000
per


145.2 145.2 135.2 133.4 134.2 134.7 122.8 119.1 122.6 119.1 135.1
138.6 138.6 126.8 123.1 121.1 114.2 96.2 86.2 81.9 77.8 85.5
86.8 86.8 81.2 80.4 81.8 84.1 78.5 80.2 82.1 79.3 87.8
82 82 77.4 73.8 70 65.2 54.7 51 47 44.4 50.2
52.7 52.7 49.8 48.9 50.4 53.3 53.4 53.3 52.9 50.4 55.7
50.9 50.9 44.8 41.8 38.9 36.5 32.4 28.9 27.5 27.2 31.2
32.5 32.5 30 30.4 31.3 34.2 34.4 33.3 32.9 32.7 36.1
30.4 30.4 25.2 23.6 21.4 20.8 18.9 17.1 16.7 17.1 20.5
20 20 18.9 19.1 19.8 21.8 21.3 20.8 21.1 21.3 22.6
18.2 18.2 15.3 13.6 12.5 12.1 11.6 11 11.3 11.8 13.6
12.8 12.8 12 12.4 12.6 13.4 12.8 12.8 13.4 13.1 14.2
11.3 11.3 9 8.5 7.7 7.5 7.3 7.5 7.6 8.1 9.3
8.3 8.3 7.7 7.6 7.5 7.7 7.7 8.2 7.9 7.9 8.5
7.3 7.3 6 5.4 5 4.9 5.2 5 5.2 5.4 5.7
5.6 5.6 5 4.4 4.3 4.5 4.7 4.8 4.8 4.6 5
5.2 5.2 4.1 3.7 3.2 3.2 3.4 3.5 3.4 3.2 3.5
3.8 3.8 3.1 2.7 2.7 2.7 3 2.9 2.8 2.7 3.3
3.5 3.5 2.6 2.3 2.1 2.1 2.3 2.1 2 1.9 2.1
2.8 2.8 2.1 1.7 1.7 1.8 1.9 1.8 1.8 1.9 2.3
2.9 2.9 1.9 1.5 1.5 1.4 1.4 1.2 1.2 1.1 1.2
2.5 2.5 1.7 1.4 1.3 1.3 1.2 1.1 1.3 1.6 1.7
2.2 2.2 1.4 1.1 1 0.8 0.8 0.7 0.7 0.7 0.7
2.4 2.4 1.5 1.2 1.2 1 1 1 1.2 1.1 1.3
2 2 1 0.8 0.6 0.6 0.5 0.4 0.5 0.5 0.5
2.5 2.5 1.4 1.3 1.1 1 1.1 1.1 1.2 1 1.1
1.7 1.7 0.8 0.5 0.5 0.4 0.4 0.4 0.4 0.4 0.4
1.5 1.5 0.9 0.9 0.8 0.8 1 1 0.8 0.8 0.7
1.1 1.1 0.6 0.4 0.4 0.4 0.4 0.3 0.4 0.3 0.3
0.8 0.8 0.5 0.4 0.4 0.4 0.4 0.3 0.3 0.3 0.2
0.6 0.6 0.4 0.3 0.2 0.3 0.3 0.2 0.2 0.2 0.2
age
80
70
60
50
40
30
20
1940
1950
1960
1970
1980
1990
2000
per

# Split the data to fit with population data

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

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

Create variables to fit with the population data

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

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

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

[1] 418  21

> gmortDK[1:6,1:6]

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

> gmortDK$per <- gmortDK$per+1900
> #
> thadx <- merge( thad, gmortDK[,c("agr","per","sex","rt")] )
> #
> thadx$E <- thadx$lex.dur * thadx$rt / 1000
> stat.table(contrast,
+            list( D = sum(lex.Xst),
+                  Y = sum(lex.dur),
+                  E = sum(E),
+                SMR = ratio(lex.Xst, E)),
+             margin = TRUE,
+               data = thadx)
 --------------------------------------------
 contrast         D        Y       E     SMR
 --------------------------------------------
 1           917.00 20045.46  214.66    4.27
 2          1022.00 31742.51  447.21    2.29

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

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

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

- Analysis of SMR is like analysis of rates:
- Replace $Y$ with $E$ — that's all! (`glm.Lexis` not usable)
- . . . it's the calculation of $E$ that is difficult