Representation of follow-up

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SPE, Tartu, Estonia,

June 2023

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

Representation of follow-up data

A cohort or follow-up study records events and risk time

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

Follow-up **data** for each individual must therefore have (at least) three pieces of information recorded:

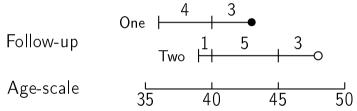
```
\begin{array}{lll} \text{Date of entry} & \text{entry} & \text{date variable} \\ \text{Date of exit} & \text{exit} & \text{date variable} \\ \text{Status at exit} & \text{fail} & \text{indicator (mostly } 0/1) \end{array}
```

These are specific for each **type** of outcome.

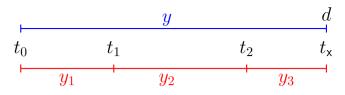
Stratification by age

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

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



- allowing rates to vary across age-bands
- how do we do the split and why is it OK?



Probability

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

$$= P(\mathsf{surv}\ t_0 o t_1 | \mathsf{entry}\ t_0)$$

$$imes P(\mathsf{surv}\ t_1 o t_2 | \mathsf{entry}\ t_1)$$

$$imes \mathrm{P}(d \ \mathsf{at} \ t_{\mathsf{x}} | \mathsf{entry} \ t_2)$$

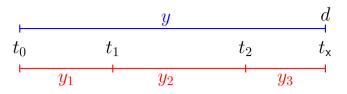
log-Likelihood

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

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

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

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



Probability log-Likelihood
$$P(d \text{ at } t_{\mathsf{x}} | \mathsf{entry} \ t_0) \qquad \qquad d \log(\lambda) - \lambda y$$

$$= P(\mathsf{surv} \ t_0 \to t_1 | \mathsf{entry} \ t_0) \qquad \qquad = 0 \log(\lambda_1) - \lambda_1 y_1$$

$$\times P(\mathsf{surv} \ t_1 \to t_2 | \mathsf{entry} \ t_1) \qquad \qquad + 0 \log(\lambda_2) - \lambda_2 y_2$$

— allows different rates (λ_i) in each interval

 $\times P(d \text{ at } t_{\mathbf{y}} | \text{entry } t_2)$

 $+d\log(\lambda_3) - \lambda_3 y_3$

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.

Example: cohort with 3 persons:

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

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

Splitting the follow-up

	subj. 1	subj. 2	subj. 3
Age at Entry: Age at eXit: Status at exit:	13.06 44.95 Dead	18.44 41.14 Alive	4.54 11.12 Dead
$Y \\ D$	31.89	22.70	6.58

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

Splitting the follow-up

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

Keeping track of calendar time too?

Follow-up intervals on several timescales

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

$$(d, y)$$
 (event, duration)

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

Follow-up data in Epi — Lexis objects I

```
> thoro[1:6.1:8]
 id sex birthdat contrast injecdat volume
                                         exitdat exitstat
      2 1916,609
                        1 1938, 791
                                       22 1976, 787
      2 1927,843
                        1 1943,906
                                      80 1966.030
  3 1 1902.778
                        1 1935,629
                                   10 1959.719
  4 1 1918.359
                        1 1936.396
                                   10 1977.307
  5 1 1902.931
                                   10 1945.387
                        1 1937 387
  6 2 1903,714
                        1 1937,316
                                       20 1944,738
 thL <- Lexis(entry = list(age = injecdat-birthdat,
                           dte = injecdat.
+
               exit = list(dte = exitdat).
+
        exit.status = as.numeric(exitstat == 1),
               data = thoro
```

Follow-up data in Epi — Lexis objects II

```
NOTE: entry.status has been set to 0 for all.
NOTE: Dropping 2 rows with duration of follow up < tol
> summary(thL, timeScales = TRUE)

Transitions:
    To
From 0 1 Records: Events: Risk time: Persons:
    0 504 1964 2468 1964 51934.08 2468

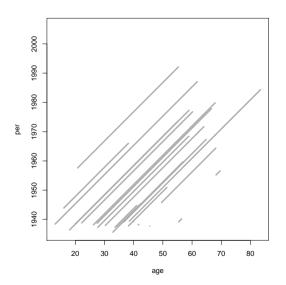
Timescales:
age dte tfi
"" "" "" ""
```

Definition of Lexis object

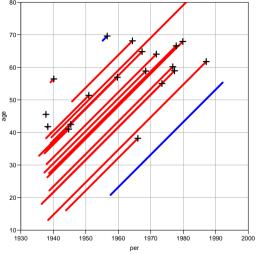
One element of entry and exit must have same name (dte).

The looks of a Lexis object

```
> thL[1:4,1:9]
            dte tfi lex.dur lex.Cst lex.Xst lex.id
1 22.18 1938.79
                      37.99
2 49.54 1945.77
                      18.59
3 68 20 1955 18
                     1.40
4 20.80 1957.61
                  0 34.52
. . .
> summary(thL)
Transitions:
     Tο
From
            1 Records:
                       Events:
                                 Risk time:
                                              Persons:
    504 1964
                  2468
                            1964
                                    51934.08
                                                  2468
```



> plot(thL, lwd=3)
Representation of follow-up (time-split)



Lexis diagram

EINLEITUNG

IN DIE

THEORIE

DEF

BEVÖLKERUNGSSTATISTIK

VON

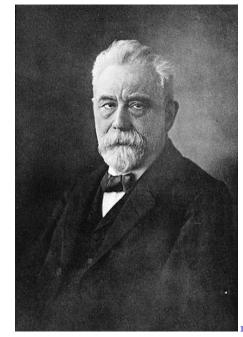
W. LEXIS

DR. DER STAATSWISSENSCHAPTEN UND DER PHILOSOPHIE O. PROFESSOR DER STATISTIK IN DORPAT.

STRASSBURG

KARL J. TRÜBNER





Splitting follow-up time

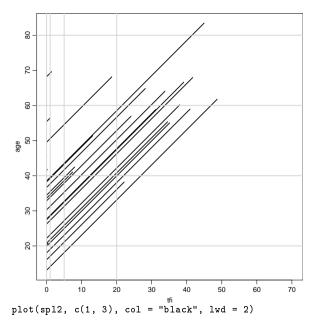
```
> spl1 <- splitLexis( thL, time.scale="age", breaks=seq(0,100,20) )</pre>
> round(spl1,1)
          dte
               tfi lex.dur lex.Cst lex.Xst
                                              id sex birthdat contrast injecdat vo
1 22.2 1938.8
               0.0
                       17.8
     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

Representation of follow-up (time-split)

. . .

Split on another timescale

```
> sp12 <- splitLexis( sp11, time.scale="tfi", breaks=c(0,1,5,20,100) )</pre>
> round( spl2, 1 )
                                                         id sex birthdat contrast inje
                   dte
                        tfi lex.dur lex.Cst lex.Xst
        1 22.2 1938.8
                         0.0
                                 1.0
                                                                   1916.6
        1 23.2 1939.8
                         1.0
                                 4.0
                                                                   1916.6
        1 27.2 1943.8
                         5.0
                                12.8
                                                                   1916.6
                                                                                       1
        1 40.0 1956.6 17.8
                                 2.2
                                                                   1916.6
        1 42.2 1958.8 20.0
                                17.8
                                                                   1916.6
        1 60.0 1976.6 37.8
                                 0.2
                                                                   1916.6
        2 49.5 1945.8
                                 1.0
                                                        640
                                                                   1896.2
        2 50.5 1946.8
                                 4.0
                                                                   1896.2
                                                                                       1
                         1.0
                                                        640
9
        2 54.5 1950.8
                        5.0
                                 5.5
                                                        640
                                                                   1896.2
                                                                                       1
10
        2 60.0 1956.2 10.5
                                 8.1
                                                        640
                                                                   1896.2
                                                                                       1
11
        3 68.2 1955.2
                       0.0
                                                     0 3425
                                                                   1887.0
                                 1.0
12
        3 69.2 1956.2
                                                       3425
                                                                   1887.0
                                                                                       1
                        1.0
                                 0.4
13
        4 20.8 1957.6
                         0.0
                                 1.0
                                                     0 4017
                                                                   1936.8
        4 21.8 1958.6
                                                     0 4017
                                                                   1936.8
                                                                                       1
14
                         1.0
                                 4.0
15
        4 25.8 1962.6
                         5.0
                                14.2
                                                       4017
                                                                   1936.8
                                                                                       1
16
        4 40.0 1976.8 19.2
                                 0.8
                                                       4017
                                                                   1936.8
                                                                                       1
17
        4 40.8 1977.6 20.0
                                14.5
                                                       4017
                                                                   1936.8
```



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

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(sp12)
Transitions:
    To
From
       0 1 Records: Events: Risk time: Persons:
  0 8250 1964 10214 1964 51934.08
                                               2468
> library(popEpi)
> splx < - splitMulti(thL, age = seq(0, 100, 20), tfi = c(0, 1, 5, 20, 100))
> summarv(splx)
Transitions:
    To
       0 1 Records: Events: Risk time: Persons:
From
  0 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) intervals
- ► 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

- $ightharpoonup d_{pi}$ events in the variable: lex.Xst & lex.Xst!=lex.Cst
- $ightharpoonup y_{pi}$ risk time: lex.dur (duration)
- Covariates are:
 - timescales (age, period, time in study)
 - 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).
                Y = sum(lex.dur).
             Rate = ratio(lex.Xst, lex.dur, 100)),
            margin = TRUE,
             data = spl2)
contrast
                             Rate
        928.00 20094.74 4.62
          1036.00 31839.35 3.25
Total 1964.00 51934.08 3.78
```

Fitting a simple model

```
contrast D Y Rate

1 928.00 20094.74 4.62
2 1036.00 31839.35 3.25

> m0 <- glm((lex.Xst==1) ~ factor(contrast) -
```

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

Fitting a simple model

```
        contrast
        D
        Y
        Rate

        1
        928.00
        20094.74
        4.62

        2
        1036.00
        31839.35
        3.25
```

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

Fitting a simple model

The wrapper glm.Lexis requires that lex.Cst and lex.Xst are factors—use factorize to make them:

...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 2		20094.74 31839.35	4.62 3.25

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

SMR

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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)

SMR (SMR) 30/ 40

Cohort rates vs. population rates: RSR

- ▶ Additive: $\lambda(a) = \delta(a) + \lambda_p(a)$
- Note that the survival (since $a=a_0$, say) is:

$$S(a) = \exp\left(-\int_{a_0}^{a} \delta(a) + \lambda_{p}(a) da\right)$$
$$= \exp\left(-\int_{a_0}^{a} \delta(a) da\right) \times S_{p}(a)$$
$$\Rightarrow r(a) = S(a)/S_{p}(a) = \exp\left(-\int_{a_0}^{a} \delta(a) da\right)$$

▶ Additive model for rates ⇔ Relative survival model.

SMR (smr) 31/ 40

Cohort rates vs. population rates: SMR

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

$$D_a \log(\lambda(a)) - \lambda(a) Y_a = D_a \log(\theta \lambda_{p}(a)) - \theta \lambda_{p}(a) Y_a$$

=
$$D_a \log(\theta) + D_a \log(\lambda_{p}(a)) - \theta(\lambda_{p}(a) Y_a)$$

▶ The constant $D_a\log(\lambda_p(a))$ does not involve θ , and so can be dropped.

SMR (smr) 32/ 40

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

$$D_a \log(\theta) - \theta(\lambda_p(a)Y_a) = D_a \log(\theta) - \theta(E_a)$$

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

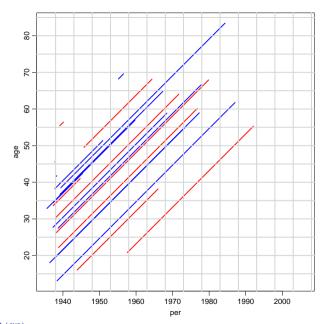
$$\hat{ heta} = \sum_a D_a / \sum_a E_a = \mathsf{Observed/Expected} = \mathsf{SMR}$$

SMR (smr) 33/ 40

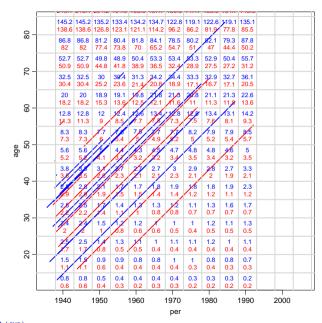
Modeling the SMR in practice

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

SMR (smr) 34/ 40



SMR (SMR) 35/40



SMR (smr) 36/ 40

Split the data to fit with population data

```
> thad <- splitMulti(thL, age=seq(0,90,5), dte=seq(1938,2038,5))</pre>
> summary( thad )
Transitions:
    To
        0 1 Records: Events: Risk time: Persons:
From
  0 21059 1939
                        1939
                  22998
                               51787.96
                                              2463
Create variables to fit with the population data
> thad$agr <- timeBand( thad, "age", "left" )</pre>
> thad$per <- timeBand( thad, "dte", "left" )</pre>
> 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
     1 25.00 1941.61 1.39 0 25 1938
     1 26.39 1943.00 3.61 0 25 1943
     1 30.00 1946.61 1.39 0 30 1943 2
     1 31.39 1948.00 3.61 0 30 1948
```

SMR (SMR) 37/ 40

```
> data( gmortDK )
> dim( gmortDK )
[1] 418 21
> gmortDK[1:6,1:6]
  agr per sex
              risk
                        dt
                                rt.
       38
            1 996019 14079
    0
                           14,135
           1 802334
       38
                      726
                            0.905
  10
       38
           1 753017
                     600
                             0.797
  15
       38
           1 773393
                       1167
                            1.509
           1 813882
                            2.495
  20
       38
                       2031
  25
      38
            1 789990 1862 2.357
> gmortDK$per <- gmortDK$per+1900</pre>
> thadx <- merge( thad, gmortDK[,c("agr","per","sex","rt")] )</pre>
> #
> thadx$E <- thadx$lex.dur * thadx$rt / 1000</pre>
```

SMR (smr) 38/ 40

```
> 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
                                      SMR.
            917.00 20045.46 214.66 4.27
          1022.00 31742.51 447.21 2.29
Total 1939.00 51787.96 661.87 2.93
```

SMR (SMR) 39/ 40

```
contrast
                                       SMR.
            917.00 20045.46 214.66 4.27
           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:
- ightharpoonup Replace Y with E that's all! (glm.Lexis not usable)
- it's the calculation of E that is difficult