Multistate models

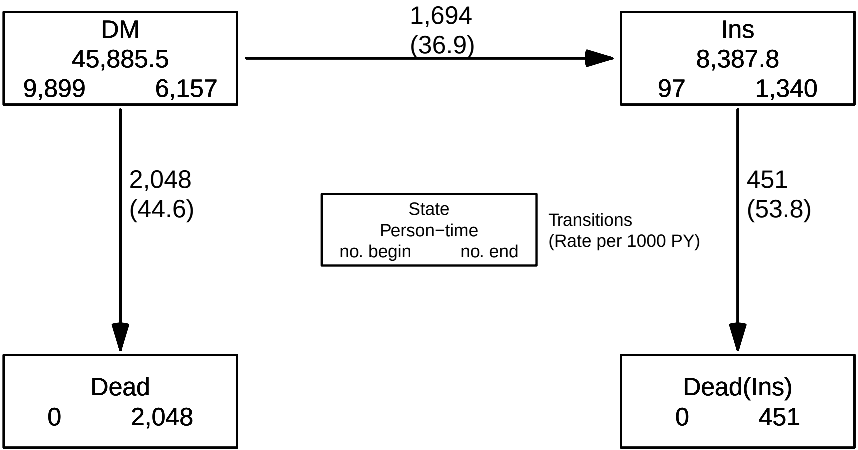
Bendix Carstensen Steno Diabetes Center Copenhagen
Herlev, Denmark
http://BendixCarstensen.com

Study Circle, 4th December 2024

http://BendixCarstensen.com/PMM — Practical Multistate Modeling

From Wednesday 4th December, 2024, 12:09

Multi-state model — 4 states, 3 transitions



Transient and absorbing states

Two types of states are normally distinguished:

- **transient** states are states from which it is possible to exit
- **absorbing** states are states from which it is impossible to exit, typically death.

Transition matrix

- Rows and columns labeled by the states that can be assumed
- The entry in row A, column B is
  the probability of state B at time t given state A at time s:

$$\mathrm{P}_{\mathtt{AB}}(s,t) = \mathrm{P}\left\{\text{state } \mathtt{B} \text{ at time } t \mid \text{state } \mathtt{A} \text{ at time } s\right\}$$

- ...so the matrix is a function of two timepoints, s and t
- time-**homogeneous** $\Rightarrow$ only function of $t - s$
  $\Rightarrow$ transition **rates** are constant
- no requirement only to consider moves **directly** from A to B.

Transition matrix

	to			
from	DM	Ins	Dead	Dead(Ins)
DM	$1 - p_{DI} - p_{DD}$	p_{DI}	p_{DD}	0
Ins	0	$1 - p_{ID}$	0	p_{ID}
Dead	0	0	1	0
Dead(Ins)	0	0	0	1

Transition matrix, $t - s = 1$ month (from boxes)

```
> # Initial state distribution
> (p0 <- c(DM=1, Ins=0, Dead=0, "Dead(Ins)"=0))
       DM       Ins      Dead Dead(Ins)
        1         0         0         0
> # Transition matrix (per month)
> Tm <- matrix(0, 4, 4)
> rownames(Tm) <- colnames(Tm) <- names(p0)
> Tm["DM","Ins"]  <- 1694 / 45885.5 / 12
> Tm["DM","Dead"] <- 2048 / 45885.5 / 12
> Tm["Ins","Dead(Ins)"] <- 451 / 8387.8 / 12
> diag(Tm) <- 1 - apply(Tm, 1, sum)
> Tm
                 DM         Ins        Dead   Dead(Ins)
DM        0.9932041 0.003076498 0.003719403 0.000000000
Ins       0.0000000 0.995519286 0.000000000 0.004480714
Dead      0.0000000 0.000000000 1.000000000 0.000000000
Dead(Ins) 0.0000000 0.000000000 0.000000000 1.000000000
```

State distribution after 1, 2,. . . months

```
> (p1 <- p0 %*% Tm)
            DM         Ins        Dead Dead(Ins)
[1,] 0.9932041 0.003076498 0.003719403         0
> (p2 <- p1 %*% Tm)
            DM         Ins        Dead    Dead(Ins)
[1,] 0.9864544 0.006118304 0.007413529 1.378491e-05
> (p3 <- p2 %*% Tm)
            DM         Ins       Dead    Dead(Ins)
[1,] 0.9797505 0.009125715 0.01108255 4.119928e-05
> (p4 <- p3 %*% Tm)
            DM        Ins       Dead  Dead(Ins)
[1,] 0.9730922 0.01209903 0.01472664 8.2089e-05
```

State distribution after 5 years

```
> pm <- p0
> for(m in 1:60) pm <- pm %*% Tm
> pm
            DM       Ins      Dead  Dead(Ins)
[1,] 0.6642173 0.1323312 0.1837742 0.01967731
```

- This relies on the **time-homogeneous** assumption — the transition probabilities are the same at any time
- assuming that only one transition occur in each time interval
- It is an approximation — if we used 1 year or 1 day intervals we would get other results
- There is an analytical solution—the matrix exponential `Exp`.

State distribution — 1 year approximation

```
> # Transition matrix (per year)
> Ty <- matrix(0, 4, 4)
> rownames(Ty) <- colnames(Ty) <- names(p0)
> Ty["DM","Ins"]  <- 1694 / 45885.5
> Ty["DM","Dead"] <- 2048 / 45885.5
> Ty["Ins","Dead(Ins)"] <- 451 / 8387.8
> diag(Ty) <- 1 - apply(Ty, 1, sum)
> py <- p0
> for(m in 1:5) py <- py %*% Ty
> py
            DM       Ins     Dead Dead(Ins)
[1,] 0.6535452 0.1395399 0.189615 0.0172998
```

State distribution — 1 day approximation

```
> # Transition matrix (per day)
> Td <- matrix(0, 4, 4)
> rownames(Td) <- colnames(Td) <- names(p0)
> Td["DM","Ins"]  <- 1694 / 45885.5 / 365
> Td["DM","Dead"] <- 2048 / 45885.5 / 365
> Td["Ins","Dead(Ins)"] <- 451 / 8387.8 / 365
> diag(Td) <- 1 - apply(Td, 1, sum)
> pd <- p0
> for(m in 1:(5*365)) pd <- pd %*% Td
> pd
```

```
            DM       Ins      Dead  Dead(Ins)
[1,] 0.6651121 0.1317354 0.1832844 0.01986808
```

State distribution after 5 years

```
> cbind(py = as.vector(py),
+       pm = as.vector(pm),
+       pd = as.vector(pd))
            py         pm         pd
[1,] 0.6535452 0.66421730 0.66511213
[2,] 0.1395399 0.13233121 0.13173536
[3,] 0.1896150 0.18377418 0.18328444
[4,] 0.0172998 0.01967731 0.01986808
```

1-year approximation is not good.

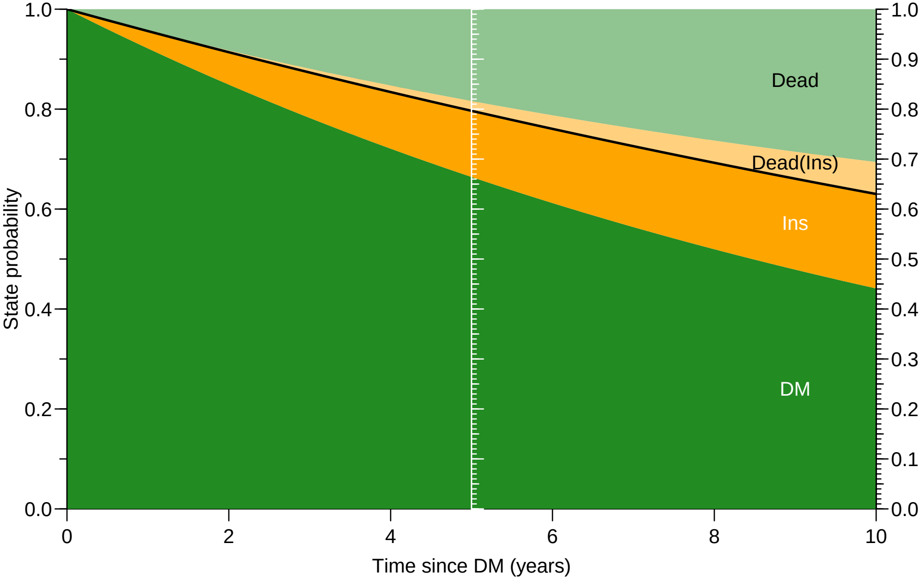
Assumption of ignorable proabability of two transitions in one interval is untenable.

Computing the state distribution by time

```
> pt <- NArray(list(month = 0:120, state = names(p0)))
> str(pt)
 logi [1:121, 1:4] NA NA NA NA NA NA ...
 - attr(*, "dimnames")=List of 2
  ..$ month: chr [1:121] "0" "1" "2" "3" ...
  ..$ state: chr [1:4] "DM" "Ins" "Dead" "Dead(Ins)"
> pt["0",] <- p0
> for(i in 1:120) pt[i+1,] <- pt[i,] %*% Tm
> pt[1:5,]
     state
month        DM         Ins        Dead    Dead(Ins)
    0 1.0000000 0.000000000 0.000000000 0.000000e+00
    1 0.9932041 0.003076498 0.003719403 0.000000e+00
    2 0.9864544 0.006118304 0.007413529 1.378491e-05
    3 0.9797505 0.009125715 0.011082551 4.119928e-05
    4 0.9730922 0.012099026 0.014726638 8.208900e-05
```

. . . still using time-homogeneous Markov model

Computing the state distribution by time



time-inhomogeneous Markov model

if transition probabilities vary by time we would replace:

```
> for(i in 1:120) pt[i+1,] <- pt[i,] %*% Tm
```

with:

```
> for (i in 1:120) pt[i+1,] <- pt[i,] %*% Tm[,,i]
```

—transition matrix depends on time (`i`)

But we still have all FU referring to the same time-scale:
`(i in 1:120)`

Semi-markov model

- Transition probabilities (and -rates) depend on time since entry to current state
- $\Rightarrow$ time is different for different persons
- $\Rightarrow$ matrix multiplication machinery does not apply
- Prediction only possible by micro-simulation (see the `simLexis` vignette in the `Epi` package

Non-markov model

- Transition probabilities (and -rates) depend on more than one time scale
- $\Rightarrow$ persons in a state are at different times on several time scales
- $\Rightarrow$ matrix multiplication machinery does not apply
- Prediction only possible by micro-simulation
  (see the `simLexis` vignette in the `Epi` package)

4 classes of multistate models

1. **Homogeneous Markov:** All transition intensities are constant over time. Allows calculation of state probabilities using the matrix exponential on the transition intensity matrix.
2. **Inhomogeneous Markov:** Transition rates vary by time but all transition rates vary along the **same** time scale. *Time-specific* transition probability matrices.
3. **Semi Markov:** Transition rates from different states vary by time since entry to the state, so along *different* time scales in different states. Micro-simulation needed.
4. **Multiple timescales:** Transition rates depend on more than one time scale, such as current age and current duration of diabetes. Micro-simulation needed.

Data, observations

- The simplest multistate model is a survival model with states `Alive` and `Dead` — one possible transition.
- The basic observation for each person is the (empirical) rate in the form (d, y), where
  d is the **event count** (0 or 1) and
  y is the **risk time**, *i.e.* the time at risk of dying.

Model

- The likelihood is the probability of seeing (d, y) as a function of the occurrence rate.
- We need a precise definition of a **theoretical** mortality rate:

$$\lambda(t) = \lim_{h \to 0} \mathrm{P}\left\{\text{death in } (t, t+h] \,|\, \text{alive at } t\right\}/h$$

Likelihood

- a person at risk from time t_e (entry) to t_x (exit)
- status at t_x is d, where $d = 0$ is alive and $d = 1$ is dead.
- choose, say, two time points, t_1, t_2 between t_e and t_x
  — Bayes' formula gives:

$$
\begin{aligned}
\mathrm{P}\left\{d \text{ at } t_x \,|\, \text{entry at } t_e\right\} = & \mathrm{P}\left\{\text{survive } (t_e, t_1] \,|\, \text{alive at } t_e\right\} \times \\
& \mathrm{P}\left\{\text{survive } (t_1, t_2] \,|\, \text{alive at } t_1\right\} \times \\
& \mathrm{P}\left\{\text{survive } (t_2, t_x) \,|\, \text{alive at } t_2\right\} \times \\
& \mathrm{P}\left\{d \text{ at } t_x \,|\, \text{alive just before } t_x\right\}
\end{aligned}
$$

…one term per interval

Likelihood contributions per interval

- more intermediate time points $\Rightarrow$ smaller intervals
- for the first three terms we just need to derive the probability of surviving a small piece of time, as a function of the mortality rate.

Likelihood from survival

- Assume that the mortality is constant over time $\lambda(t) = \lambda$.
- The definition of a rate

$$\lambda(t) = \lim_{h \to 0} \mathrm{P}\left\{\text{death in } (t, t+h] \,|\, \text{alive at } t\right\}/h$$

leads to (conditional on being alive at t):

$$\begin{aligned} &\mathrm{P}\left\{\text{death during } (t, t+h]\right\} \approx \lambda h \\ &\Rightarrow \mathrm{P}\left\{\text{survive } (t, t+h]\right\} \approx 1 - \lambda h \end{aligned}$$

Likelihood from survival

- a single person's survival (risk time) time $y = t_x - t_e$
- subdivided in N intervals, each of length $h = y/N$
- $\Rightarrow$ survival probability for the entire span from t_e to t_x is the product of probabilities of surviving each of the N small intervals, conditional on being alive at the beginning of each interval:

$$\mathrm{P}\left\{\text{survive } t_e \text{ to } t_x\right\} \approx (1 - \lambda h)^N = \left(1 - \frac{\lambda y}{N}\right)^N \to \exp(-\lambda y)$$

for $N \to \infty$

Likelihood from event

- event at the end of the last interval for a person
  $\Rightarrow$ likelihood contribution:
  probability of dying in the last tiny instant (of length ϵ, say)
- by the definition of the rate, this is $\lambda\epsilon$, and hence the log-likelihood contribution is $\log(\lambda\epsilon) = \log(\lambda) + \log(\epsilon)$.
- since $d_i = 1$ only for the last interval if an event occurs and 0 otherwise, we can say that all intervals contribute

$$d_i\big(\log(\lambda) + \log(\epsilon)\big)$$

one person's log-likelihood contribution

- The total likelihood for one person is the product of all these terms from the follow-up intervals (i) for the person:
- $\Rightarrow$ log-likelihood, $\ell\big(\lambda|(d_i, y_i)\big)$ is a sum over intervals:

$$\ell(\lambda) = \sum_i -\lambda y_i + \sum_i d_i \big(\log(\lambda) + \log(\epsilon)\big)$$
$$= \sum_i \big(d_i \log(\lambda) - \lambda y_i\big) + \sum_i d_i \log(\epsilon)$$

model and log-likelihood from one person

$$\sum_i \left(d_i \log(\lambda) - \lambda y_i\right)$$

- this is also the log-likelihood for
  independent Poisson variates d_i with mean λy_i
- . . . but the (d_i, y_i) contributions from a single person are **neither independent nor Poisson**
  . . . merely an algorithmic convenience.
- **Same** likelihood, but
  different models and **different** observations

Parametric rate models

- parametric modeling of **rates** allows different λ_is in each interval
  —assuming that rates are constant **within** each interval
- (age-)**groups** are irrelevant, the actual age at the start of the interval is used as a **quantitative** variable
- (duration-)**groups** are irrelevant, the actual duration at the start of the interval is used as a **quantitative** variable
- note that the values of the quantitative variables describing the λ_is need not be in a pre-defined finite set

Demography: Scales of inference

-1. Occurrence rates
—the scale of **observed** register data, (d, y) (empirical rate), measured in time^{-1} (events per person-time)

0. State probabilities (survival function)
—the **integral** of rates w.r.t. time
—requires an origin (such as date of diagnosis)
measured in time^{0} (dimensionless)

1. Sojourn times (time spent in a state)
—the **integral** of state probabilities w.r.t. time
—requires an origin and endpoint
measured in time^{1}

Demographic quantities—functions of time

- occurrence rate:

$$\lambda(t) = \lim_{h \to 0} \mathrm{P}\{\text{event in } (t, t+h) \,|\, \text{alive at } t\}/h$$

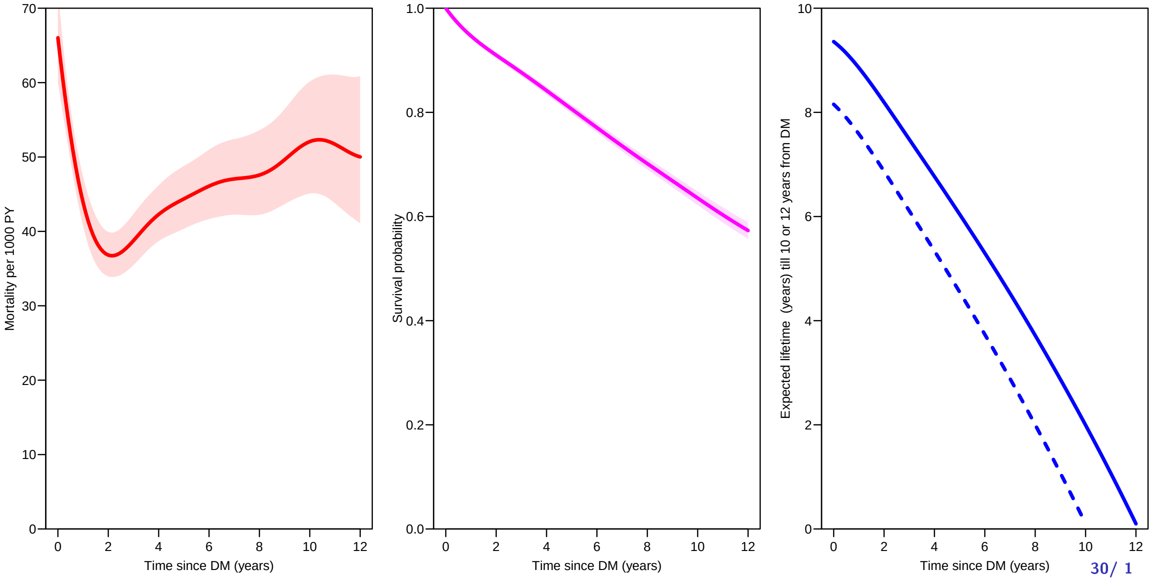
- survival probability (since time a):

$$\mathrm{S}_a(t) = \exp\left(-\int_a^t \lambda(u)\,\mathrm{d}u\right)$$

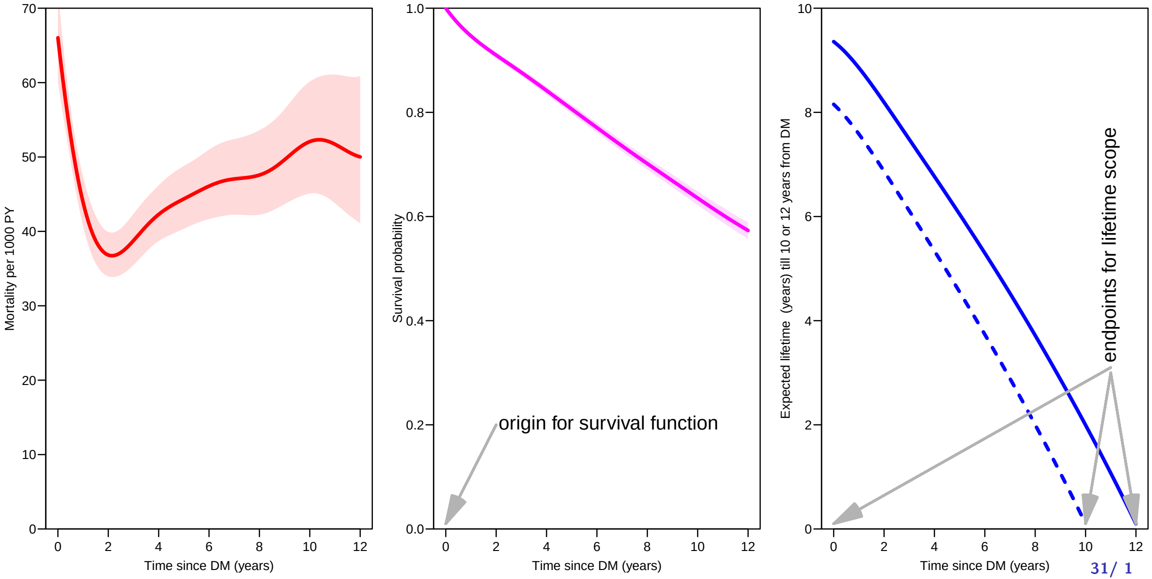
- sojourn time (between t and b)
  (restricted mean survival time to b, RMST):

$$\mathrm{L}(t) = \int_t^b \mathrm{S}_t(u)\,\mathrm{d}u$$

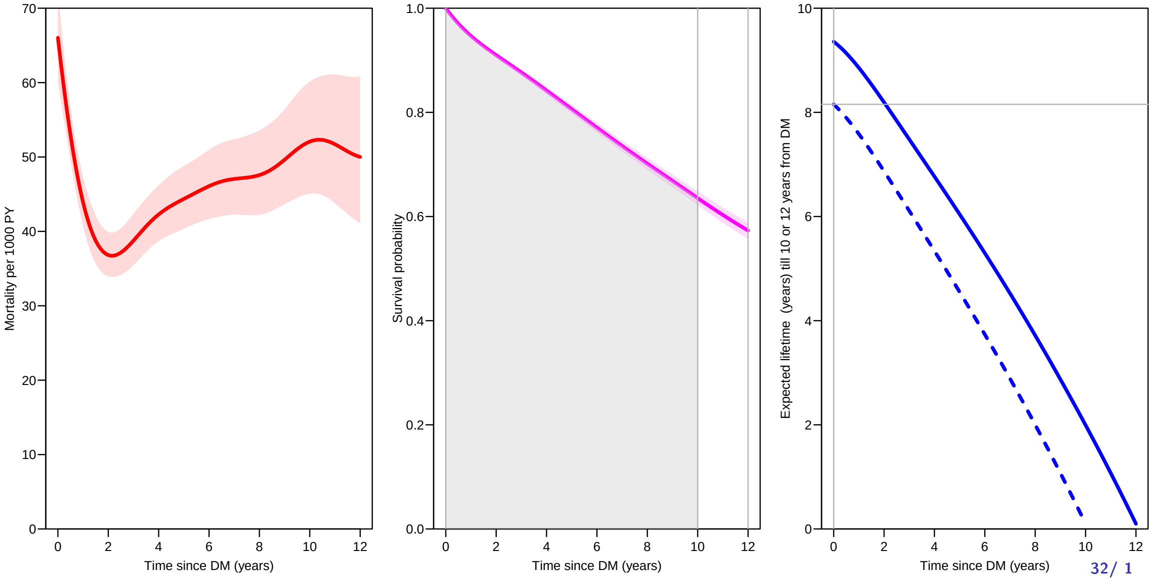
Mortality / survival / life time after DM



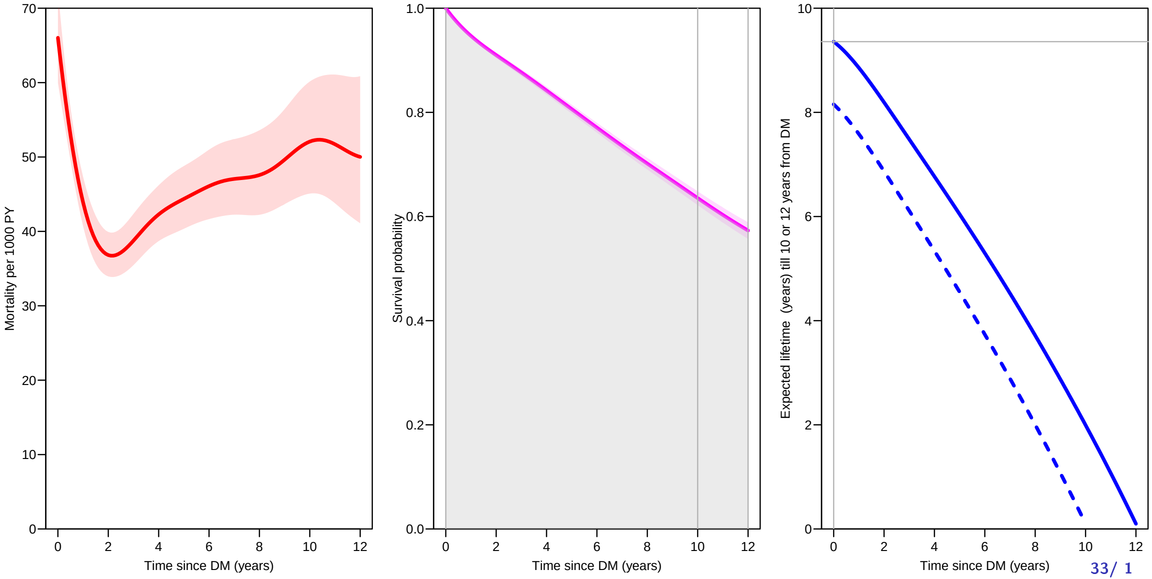
Mortality / survival / life time after DM



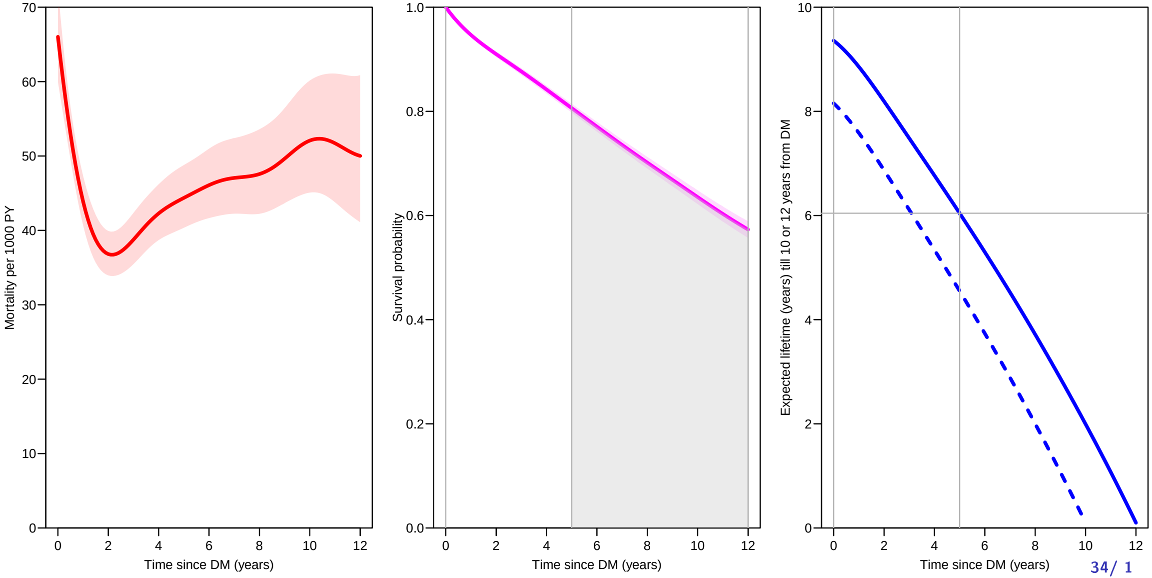
Mortality / survival / life time after DM



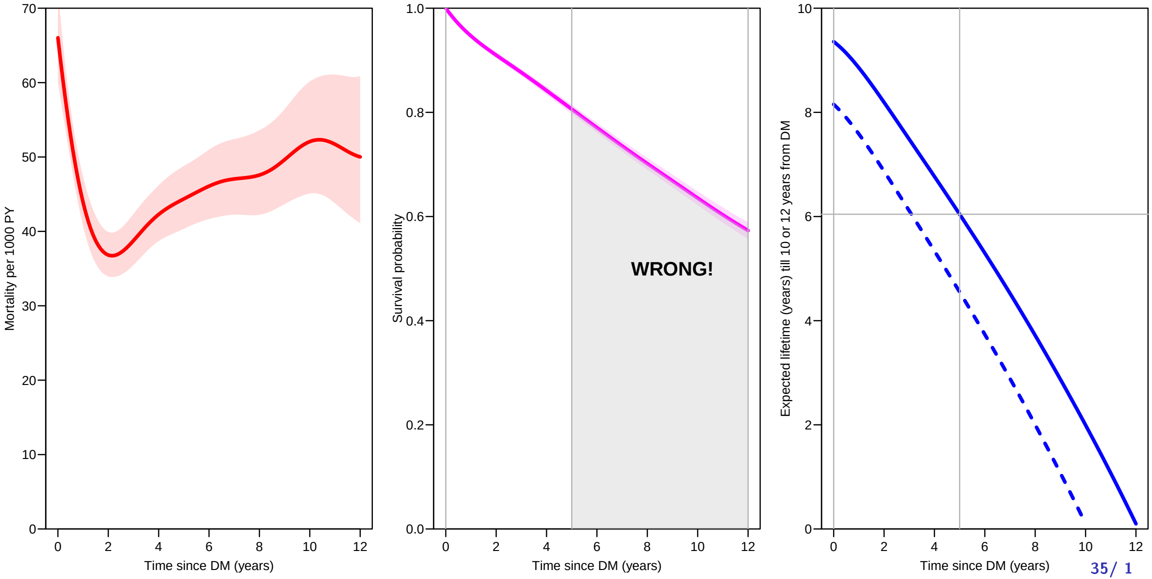
Mortality / survival / life time after DM



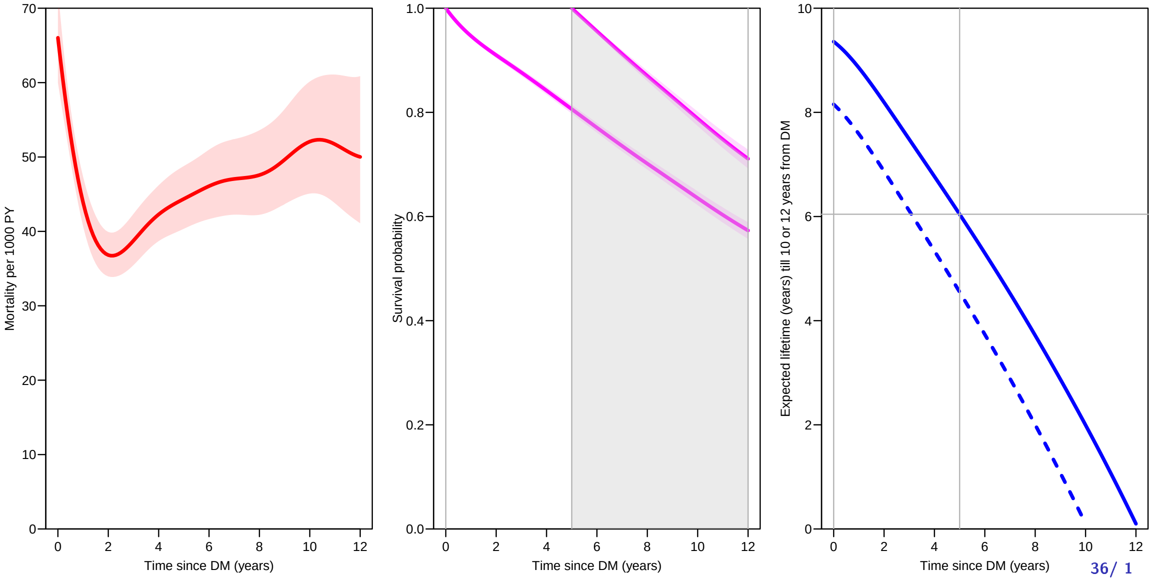
Mortality / survival / life time after DM



Mortality / survival / life time after DM



Mortality / survival / life time after DM



How does follow-up look in a dataset

- One record per time **interval** (where nothing happens)
- Things happen at the **end** of the interval,
  the interval FU time belongs in a particular **state**, e.g.:
  - noDM / T1 / T2
  - noCKD / CKD
  - no comorb. / 1 comorb. / 2 comorb. / 3 comorb. / . . .

How does follow-up look in a dataset

- Intervals may further be classified by **time-varying** variables:
  - quantitative deterministic variables (time scales):
    age, date of follow up, diabetes duration
  - quantitative random variables: HbA_{1c}, cholesterol, ...
  - categorical random variables: parity, marital status
- States are a special type of time varying covariates:
  targets of demographic measures (probability, sojourn time)

```
> library(Epi)
> data(DMlate)
> DMlate[13:19,]
        sex    dobth     dodm   dodth    dooad    doins      dox
119305    M 1938.107 1997.461 1998.35       NA       NA 1998.350
188248    F 1979.864 1999.684      NA       NA       NA 2009.997
38336     M 1944.420 2002.550      NA       NA 2005.354 2009.997
368534    F 1962.482 2000.355      NA 2001.559       NA 2009.997
139497    F 1956.439 1995.544      NA       NA       NA 2009.997
132331    M 1935.024 1996.746      NA 1997.915 2005.995 2009.997
228434    F 1949.622 2006.783      NA 2006.783       NA 2009.997
```

Each record: relevant dates for a person followed from date of diabetes till death or 2009-12-31 (end of study).

—combination of several registers

Total follow-up of diabetes ptt.

In terms of follow-up we must define:

- Entry time: `doDM`
- Exit time: `dox`
- Event death: `dodth` = `dox`

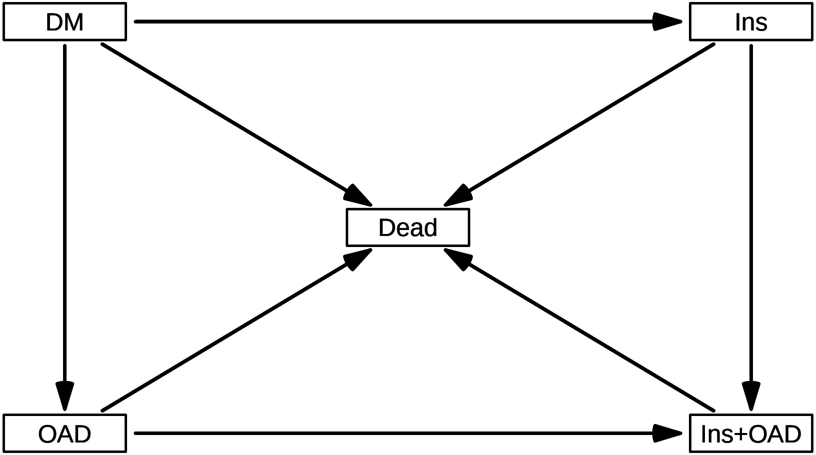
Intermediate register events

Other dates specify occurrence of intermediate events

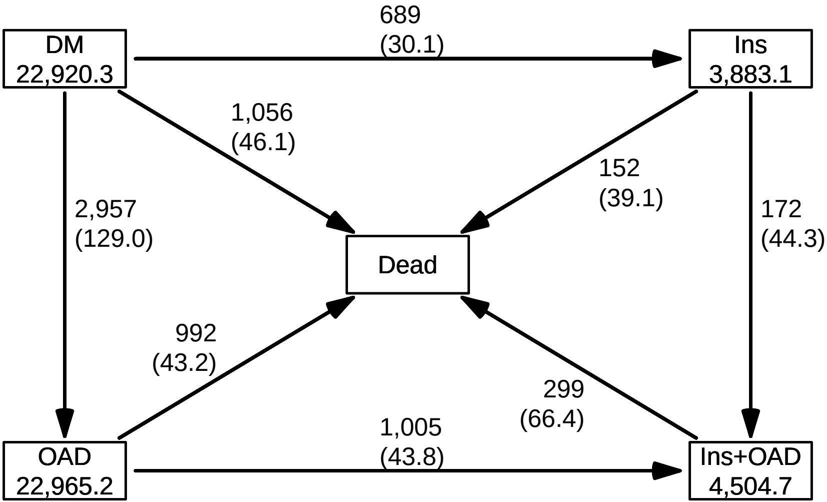
- start of OAD drugs at `doOAD`
- start of insulin at `doIns`
- possible states:
  - `DM`, no drug
  - `OAD` alone
  - `Ins` alone
  - both `OAD` & `Ins`
  - or:
    - `OAD` after `Ins`
    - `Ins` after `OAD`
  - `Dead`

States are not derived from data, they are defined by the investigator

Multi-state model — 5 states, 8 transitions



Multi-state data



Practical representation of follow-up

- provide an overview of the follow-up
- provide analytical possibility for **rate** models:
  modeling on the observation scale (observed rates (d, y))

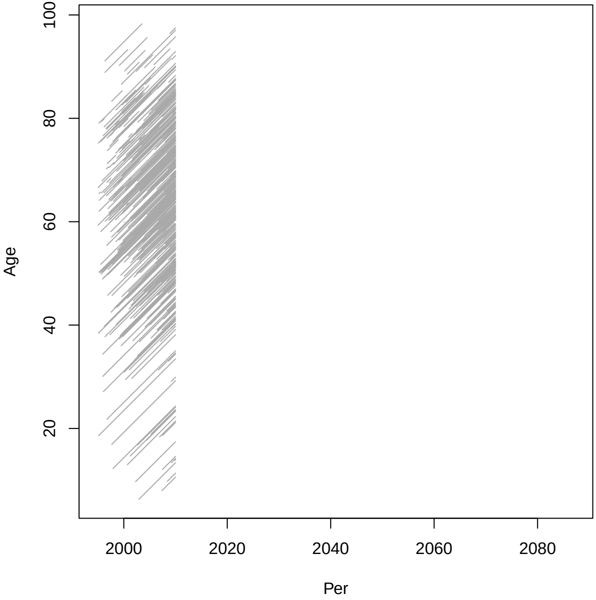
Multi-state data representation with Lexis

```
> dmL <- Lexis(entry = list(Per = dodm,
+                          Age = dodm - dobth,
+                        DMdur = 0 ),
+               exit = list(Per = dox),
+        exit.status = factor(!is.na(dodth),
+                             labels = c("DM", "Dead")),
+               data = DMlate)

NOTE: entry.status has been set to "DM" for all.
NOTE: Dropping  4  rows with duration of follow up < tol

> summary(dmL)

Transitions:
     To
From    DM Dead  Records:  Events: Risk time:  Persons:
  DM 7497 2499      9996     2499   54273.27      9996
```

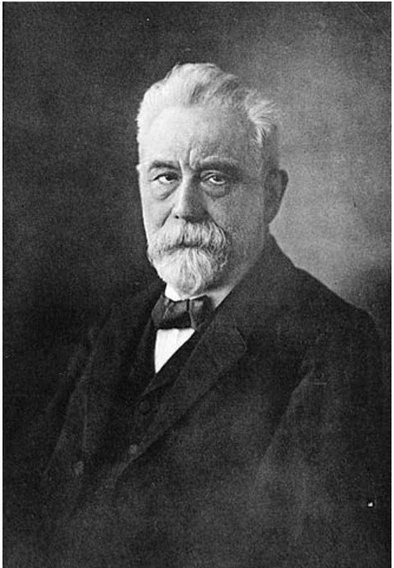
Multiple time scales: `Per`, `Age`, `DMdur`

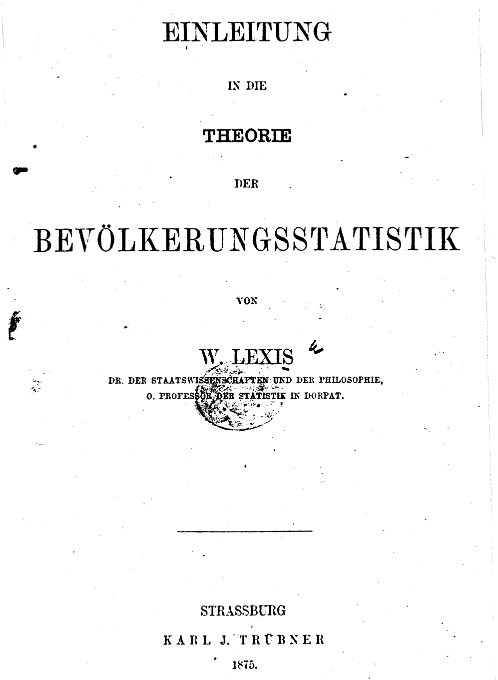
A Lexis diagram

```
> plot(dmL)
```



Wilhelm Lexis





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.

Multi-state data representation with Lexis

```
> dmIO <- mcutLexis(dmL,
+                   wh = c("dooad", "doins"),
+            timescale = "Per",
+           new.states = c("OAD", "Ins"),
+           seq.states = FALSE,
+        ties.resolve = 1/365.25)
```

```
NOTE: Precursor states set to DM
NOTE: 15 records with tied events times resolved (adding 0.002737851 random unifo
      so results are only reproducible if the random number seed was set.
```

```
> summary(dmIO)
```

```
Transitions:
     To
From        DM Dead  OAD  Ins Ins+OAD  Records:  Events: Risk time:  Persons:
  DM      2830 1056 2957  689       0      7532     4702    22920.25      7532
  OAD        0  992 3327    0    1005      5324     1997    22965.23      5324
  Ins        0  152    0  462     172       786      324     3883.06       786
  Ins+OAD    0  299    0    0     878      1177      299     4504.73      1177
  Sum     2830 2499 6284 1151    2055     14819     7322    54273.27      9996
```

```
lex.id     Per   Age DMdur lex.dur lex.Cst lex.Xst
     2 2003.31 64.09     0    6.69      DM      DM
    15 2002.55 58.13     0    7.45      DM      DM
    18 1996.75 61.72     0   13.25      DM      DM
   770 1995.22 79.25     0    8.31      DM    Dead
```

```
lex.id     Per   Age DMdur lex.dur lex.Cst lex.Xst
     2 2003.31 64.09  0.00    4.14      DM     OAD
     2 2007.45 68.23  4.14    2.55     OAD     OAD
lex.id     Per   Age DMdur lex.dur lex.Cst lex.Xst
    15 2002.55 58.13   0.0    2.80      DM     Ins
    15 2005.35 60.93   2.8    4.64     Ins     Ins
lex.id     Per   Age DMdur lex.dur lex.Cst lex.Xst
    18 1996.75 61.72  0.00    1.17      DM     OAD
    18 1997.92 62.89  1.17    8.08     OAD Ins+OAD
    18 2005.99 70.97  9.25    4.00 Ins+OAD Ins+OAD
lex.id     Per   Age DMdur lex.dur lex.Cst lex.Xst
   770 1995.22 79.25  0.00    0.27      DM     Ins
   770 1995.49 79.52  0.27    0.15     Ins Ins+OAD
   770 1995.64 79.67  0.42    7.89 Ins+OAD    Dead
```

`lex.Cst` is the Current state   `lex.Xst` is the eXit state

Multistate model: total (log-)likelihood

The log-likelihood contribution from a single person has:

- contributions to the log-likelihood for each state visited
- ...one term for each possible exit from the state
- with the same y, but $d = 1\{\mathtt{A}\}, 1\{\mathtt{B}\}$, etc.
- If the model assumes **constant** rates, log-likelihood terms are of the form $d\log(\lambda) - \lambda y$
  —a Poisson log-likelihood for variate d with mean λy
- $\Rightarrow$ total log-likelihood for a multistate model is a sum of terms, one per possible transition between states.
- a person only contributes terms from states actually visited

Multistate model data representation

- If all transition times are known (register data):
  - one record per follow-up interval (transient states)
    —representation of follow-up—`Epi` and `survival` package
    "Andersen-Gill" representation
  - one record per likelihood term (transitions)
    stacked data—`mstate` package
- state occupancy known at (some arbitrary) times
  (person `p` is in state `s` at time `t`)
  "prevalence", panel data—`msm` package

We stick to representation of follow-up time
—the most natural representation for register-based data

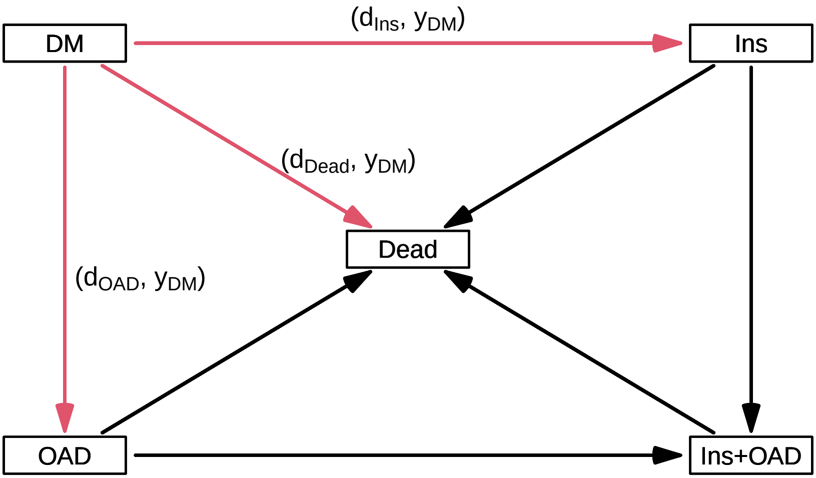
Likelihood for multistate transition rates

- assume all transitions and -times known exactly
- likelihood from one person is a **product** of terms with λ as argument
- $\Rightarrow$ log-likelihood a **sum** of terms like:

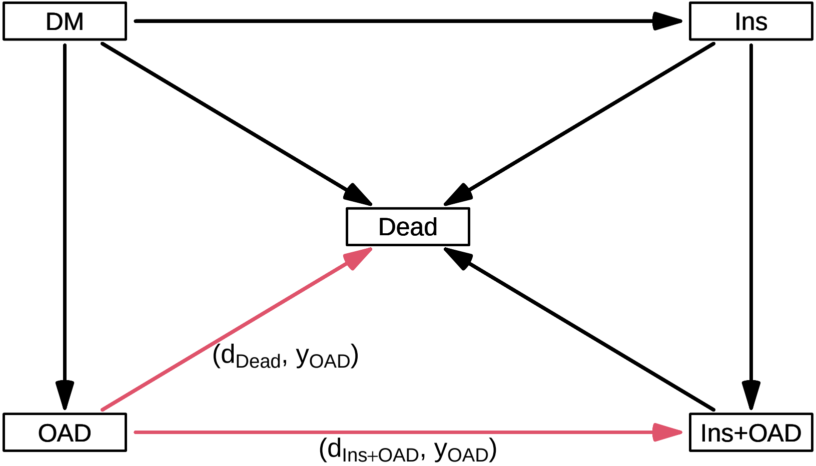
$$d \log(\lambda) - \lambda y$$

- —one term for each **possible** transition between states.
- for state `DM` **one** record but
  three likelihood terms, different ds, same y

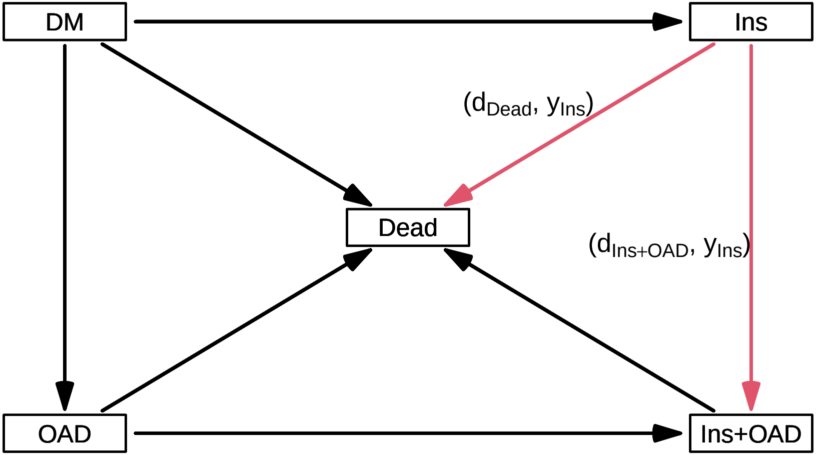
Total multi-state likelihood — 5 states, 8 transitions



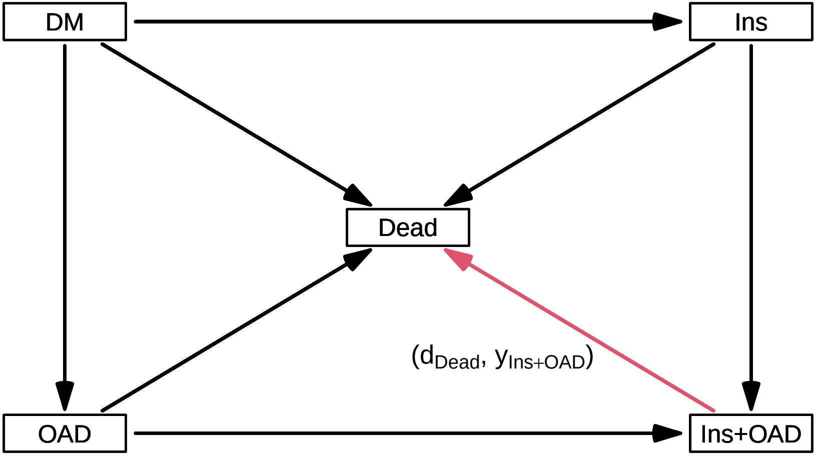
Total multi-state likelihood — 5 states, 8 transitions



Total multi-state likelihood — 5 states, 8 transitions



Total multi-state likelihood — 5 states, 8 transitions



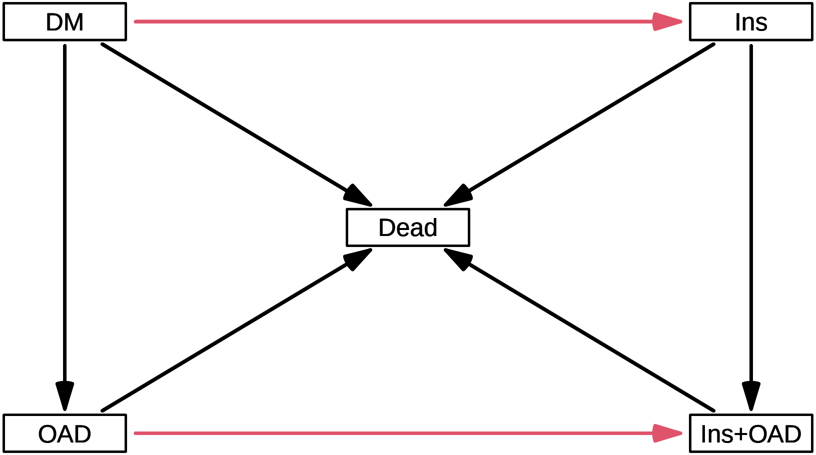
Separate models for transition rates

- For rates in the same model: common parameters possible
  e.g. same age effect for different rates
- `Lexis` represents FU-time—**not** likelihood terms
- $\Rightarrow$ analysis of a model for different rates from **different** states can be done based on a `Lexis` object
- different subsets of transition rates in different models
- for a complete model, any transition rate must be in precisely one model

Separate models for transition rates

- A model for different rates from **the same** state requires a **stacked** data frame (multiple records with the same y)
- ...but this is hardly ever relevant, e.g.:
  - do not expect age effect to be the same for rate of `OAD` and `Ins`
  - in practise only rates from **different** origin states are analysed together, such as `Ins` rates from `DM` resp. `OAD`

Partial multi-state likelihood — rates of `Ins`



Modeling rates

- Poisson likelihood is for constant rates:
- $\Rightarrow$ model restricted to constant rate within each FU-record
- remedy: split records in many records with shorter length
  —so short that constant rates in intervals is reasonable
- `splitLexis` or `splitMulti` (from `popEpi` package)
- many records with `lex.Cst` = `lex.Xst`
- include timescales in models as **quantitative** variables

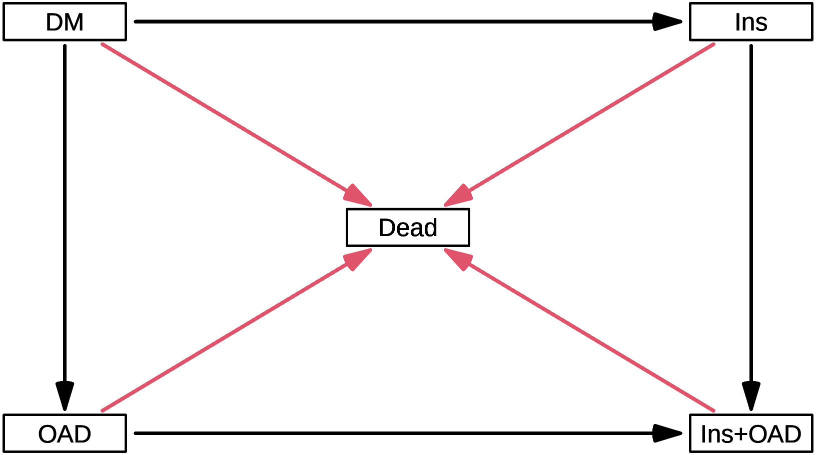
```
> summary(dmIO)

Transitions:
     To
From         DM Dead  OAD  Ins Ins+OAD  Records:  Events: Risk time:  Persons:
  DM       2830 1056 2957  689       0      7532     4702   22920.25      7532
  OAD         0  992 3327    0    1005      5324     1997   22965.23      5324
  Ins         0  152    0  462     172       786      324    3883.06       786
  Ins+OAD     0  299    0    0     878      1177      299    4504.73      1177
  Sum      2830 2499 6284 1151    2055     14819     7322   54273.27      9996

> sIO <- splitLexis(dmIO, seq(0, 20, 0.5), "DMdur")
> summary(sIO)

Transitions:
     To
From          DM Dead   OAD  Ins Ins+OAD  Records:  Events: Risk time:  Persons:
  DM       45467 1056  2957  689       0     50169     4702   22920.25      7532
  OAD          0  992 47830    0    1005     49827     1997   22965.23      5324
  Ins          0  152     0 8036     172      8360      324    3883.06       786
  Ins+OAD      0  299     0    0    9844     10143      299    4504.73      1177
  Sum      45467 2499 50787 8725   11021    118499     7322   54273.27      9996
```

```
> print(subset(sIO, lex.id == 15, select = c(wh, "dooad", "doins")))
 lex.id     Per   Age DMdur lex.dur lex.Cst lex.Xst dooad   doins
     15 2002.55 58.13   0.0    0.50      DM      DM    NA 2005.35
     15 2003.05 58.63   0.5    0.50      DM      DM    NA 2005.35
     15 2003.55 59.13   1.0    0.50      DM      DM    NA 2005.35
     15 2004.05 59.63   1.5    0.50      DM      DM    NA 2005.35
     15 2004.55 60.13   2.0    0.50      DM      DM    NA 2005.35
     15 2005.05 60.63   2.5    0.30      DM     Ins    NA 2005.35
     15 2005.35 60.93   2.8    0.20     Ins     Ins    NA 2005.35
     15 2005.55 61.13   3.0    0.50     Ins     Ins    NA 2005.35
     15 2006.05 61.63   3.5    0.50     Ins     Ins    NA 2005.35
     15 2006.55 62.13   4.0    0.50     Ins     Ins    NA 2005.35
     15 2007.05 62.63   4.5    0.50     Ins     Ins    NA 2005.35
     15 2007.55 63.13   5.0    0.50     Ins     Ins    NA 2005.35
     15 2008.05 63.63   5.5    0.50     Ins     Ins    NA 2005.35
     15 2008.55 64.13   6.0    0.50     Ins     Ins    NA 2005.35
     15 2009.05 64.63   6.5    0.50     Ins     Ins    NA 2005.35
     15 2009.55 65.13   7.0    0.45     Ins     Ins    NA 2005.35
```

```
> print(subset(sIO, lex.id == 18, c(wh, "dooad", "doins")))
 lex.id     Per   Age DMdur lex.dur lex.Cst lex.Xst   dooad   doins
     18 1996.75 61.72  0.00    0.50      DM      DM 1997.92 2005.99
     18 1997.25 62.22  0.50    0.50      DM      DM 1997.92 2005.99
     18 1997.75 62.72  1.00    0.17      DM     OAD 1997.92 2005.99
     18 1997.92 62.89  1.17    0.33     OAD     OAD 1997.92 2005.99
     18 1998.25 63.22  1.50    0.50     OAD     OAD 1997.92 2005.99
     18 1998.75 63.72  2.00    0.50     OAD     OAD 1997.92 2005.99
     18 1999.25 64.22  2.50    0.50     OAD     OAD 1997.92 2005.99
     18 1999.75 64.72  3.00    0.50     OAD     OAD 1997.92 2005.99
     18 2000.25 65.22  3.50    0.50     OAD     OAD 1997.92 2005.99
     18 2000.75 65.72  4.00    0.50     OAD     OAD 1997.92 2005.99
     18 2001.25 66.22  4.50    0.50     OAD     OAD 1997.92 2005.99
     18 2001.75 66.72  5.00    0.50     OAD     OAD 1997.92 2005.99
     18 2002.25 67.22  5.50    0.50     OAD     OAD 1997.92 2005.99
     18 2002.75 67.72  6.00    0.50     OAD     OAD 1997.92 2005.99
     18 2003.25 68.22  6.50    0.50     OAD     OAD 1997.92 2005.99
     18 2003.75 68.72  7.00    0.50     OAD     OAD 1997.92 2005.99
     18 2004.25 69.22  7.50    0.50     OAD     OAD 1997.92 2005.99
     18 2004.75 69.72  8.00    0.50     OAD     OAD 1997.92 2005.99
     18 2005.25 70.22  8.50    0.50     OAD     OAD 1997.92 2005.99
     18 2005.75 70.72  9.00    0.25     OAD Ins+OAD 1997.92 2005.99
     18 2005.99 70.97  9.25    0.25 Ins+OAD Ins+OAD 1997.92 2005.99
     18 2006.25 71.22  9.50    0.50 Ins+OAD Ins+OAD 1997.92 2005.99
```

```
> print(subset(sIO, lex.id == 18, c(wh, "dooad", "doins"))[-(1:16),])
 lex.id     Per   Age DMdur lex.dur lex.Cst lex.Xst   dooad   doins
     18 2004.25 69.22  7.50    0.50     OAD     OAD 1997.92 2005.99
     18 2004.75 69.72  8.00    0.50     OAD     OAD 1997.92 2005.99
     18 2005.25 70.22  8.50    0.50     OAD     OAD 1997.92 2005.99
     18 2005.75 70.72  9.00    0.25     OAD Ins+OAD 1997.92 2005.99
     18 2005.99 70.97  9.25    0.25 Ins+OAD Ins+OAD 1997.92 2005.99
     18 2006.25 71.22  9.50    0.50 Ins+OAD Ins+OAD 1997.92 2005.99
     18 2006.75 71.72 10.00    0.50 Ins+OAD Ins+OAD 1997.92 2005.99
     18 2007.25 72.22 10.50    0.50 Ins+OAD Ins+OAD 1997.92 2005.99
     18 2007.75 72.72 11.00    0.50 Ins+OAD Ins+OAD 1997.92 2005.99
     18 2008.25 73.22 11.50    0.50 Ins+OAD Ins+OAD 1997.92 2005.99
     18 2008.75 73.72 12.00    0.50 Ins+OAD Ins+OAD 1997.92 2005.99
     18 2009.25 74.22 12.50    0.50 Ins+OAD Ins+OAD 1997.92 2005.99
     18 2009.75 74.72 13.00    0.25 Ins+OAD Ins+OAD 1997.92 2005.99
```

Multi-state likelihood — mortality rates



Mortality rates

```
> # prior to Epi_2.58 this was glm.Lexis
> mdth <- glmLexis(sIO, ~ Ns(DMdur, knots=c(0,1,3,6,10)) + lex.Cst,
+                   to = "Dead")

stats::glm Poisson analysis of Lexis object sIO with log link:
Rates for transitions:
DM->Dead
OAD->Dead
Ins->Dead
Ins+OAD->Dead

> round(ci.exp(mdth), 3)

                                    exp(Est.)  2.5% 97.5%
(Intercept)                             0.070 0.063 0.078
Ns(DMdur, knots = c(0, 1, 3, 6, 10))1   0.614 0.514 0.734
Ns(DMdur, knots = c(0, 1, 3, 6, 10))2   0.808 0.691 0.945
Ns(DMdur, knots = c(0, 1, 3, 6, 10))3   0.337 0.253 0.450
Ns(DMdur, knots = c(0, 1, 3, 6, 10))4   0.997 0.880 1.129
lex.CstOAD                              0.970 0.889 1.059
lex.CstIns                              0.878 0.740 1.042
lex.CstIns+OAD                          1.504 1.312 1.725
```

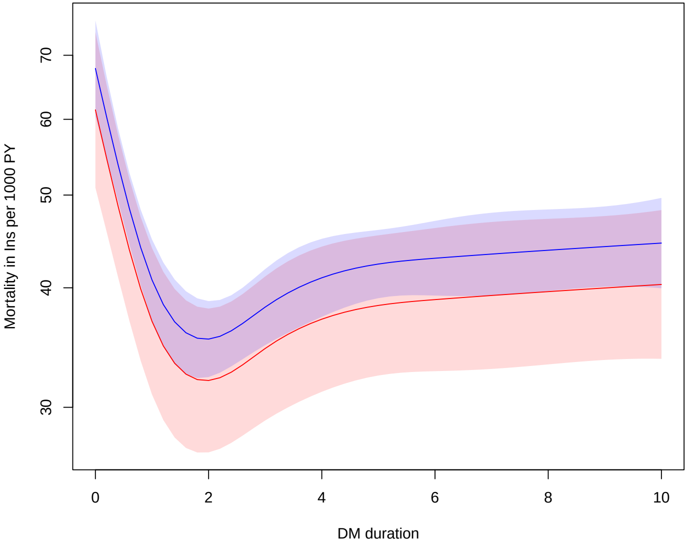
Mortality rates coxph— who cares about DMdur

```
> # prior to Epi_2.58 this was coxph.Lexis
> cdth <- coxphLexis(dmIO, DMdur ~ lex.Cst, to = "Dead")

survival::coxph analysis of Lexis object dmIO:
Rates for transitions:
DM->Dead
OAD->Dead
Ins->Dead
Ins+OAD->Dead
Baseline timescale: DMdur

> round(cbind(ci.exp(cdth)[-1,],
+              ci.exp(mdth, subset = "lex")), 3)

               exp(Est.)  2.5% 97.5% exp(Est.)  2.5% 97.5%
lex.CstOAD         0.982 0.899 1.072     0.970 0.889 1.059
lex.CstIns         0.891 0.751 1.058     0.878 0.740 1.042
lex.CstIns+OAD     1.519 1.324 1.742     1.504 1.312 1.725
```

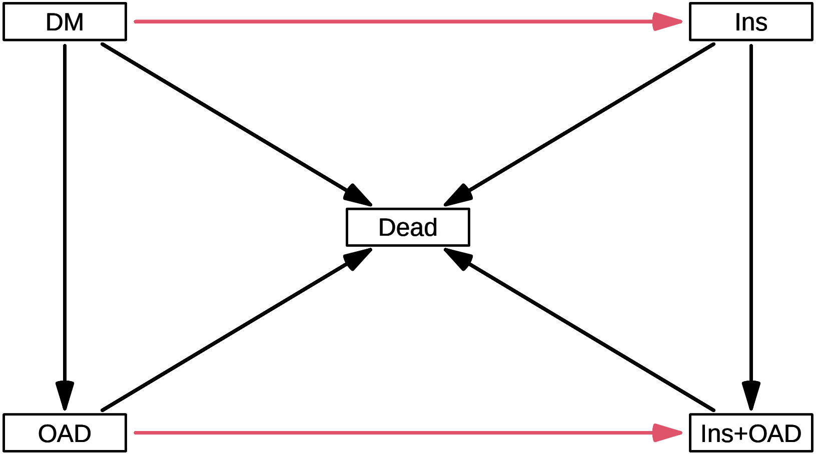
Estimated mortality rates

```
> ni <- data.frame(DMdur = seq(0, 10, 0.2), lex.Cst = "Ins")
> no <- data.frame(DMdur = seq(0, 10, 0.2), lex.Cst = "OAD")
> pdf("./graph/morti.pdf", width = 8)
> matshade(ni$DMdur, cbind(ci.pred(mdth, ni),
+                          ci.pred(mdth, no)) * 1000,
+                    plot = TRUE, col = c("red", "blue"),
+                    log = "y",
+                    xlab = "DM duration",
+                    ylab = "Mortality in Ins per 1000 PY")
> dev.off()

null device
          1
```

Mortality rates in Ins



Multi-state likelihood — rates of `Ins`



Rates of insulin uptake

```
> mins <- glmLexis(sIO, ~ Ns(DMdur, knots=c(0,1,3,6,10)) + lex.Cst,
+                    from = c("DM" ,"OAD"),
+                      to = c("Ins","Ins+OAD"))
```

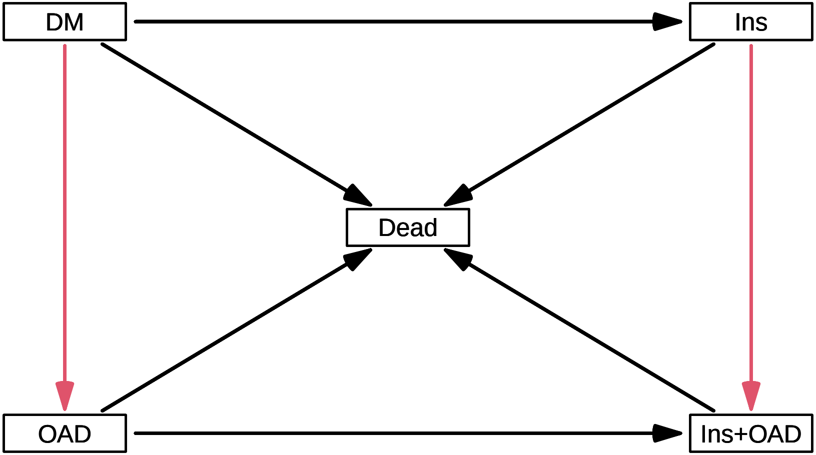
```
stats::glm Poisson analysis of Lexis object sIO with log link:
Rates for transitions:
DM->Ins
OAD->Ins+OAD
```

```
> round(ci.exp(mins), 3)
```

```
                                        exp(Est.)  2.5% 97.5%
(Intercept)                                 0.114 0.104 0.125
Ns(DMdur, knots = c(0, 1, 3, 6, 10))1      0.215 0.169 0.272
Ns(DMdur, knots = c(0, 1, 3, 6, 10))2      0.535 0.437 0.653
Ns(DMdur, knots = c(0, 1, 3, 6, 10))3      0.011 0.008 0.015
Ns(DMdur, knots = c(0, 1, 3, 6, 10))4      1.636 1.376 1.944
lex.CstOAD                                 1.766 1.599 1.950
```

OAD users are 1.8 times more likely to start on insulin

Multi-state likelihood — rates of OAD



Rates of oral drug uptake—incidence of OAD

```
> moad <- glmLexis(sIO, ~ Ns(DMdur, knots=c(0,1,3,6,10)) + lex.Cst,
+                   from = c("DM" ,"Ins"),
+                     to = c("OAD","Ins+OAD"))
```

```
stats::glm Poisson analysis of Lexis object sIO with log link:
Rates for transitions:
DM->OAD
Ins->Ins+OAD
```

```
> round(ci.exp(moad), 3)
```

```
                                   exp(Est.)  2.5% 97.5%
(Intercept)                            0.460 0.437 0.485
Ns(DMdur, knots = c(0, 1, 3, 6, 10))1  0.292 0.243 0.351
Ns(DMdur, knots = c(0, 1, 3, 6, 10))2  0.211 0.170 0.263
Ns(DMdur, knots = c(0, 1, 3, 6, 10))3  0.011 0.008 0.013
Ns(DMdur, knots = c(0, 1, 3, 6, 10))4  0.400 0.330 0.485
lex.CstIns                             0.468 0.401 0.546
```

Insulin users are half as likely as non-users to start OAD

what is glmLexis

```
> glmLexis(sIO, ~ Ns(DMdur, knots=c(0,1,3,6,10)) + lex.Cst,
+                  from = c("DM" ,"Ins"),
+                    to = c("OAD","Ins+OAD"))
```

is a wrapper for

```
> glm(cbind(lex.Xst %in% c("OAD","Ins+OAD") & lex.Xst != lex.Cst,
+           lex.dur)
+     ~ Ns(DMdur, knots=c(0,1,3,6,10)) + lex.Cst,
+     family = poisreg,
+     data = subset(sIO, lex.Cst %in% c("DM" ,"Ins")))
```

. . . note the poisreg family from Epi

What not to do

```
> mDM <- glmLexis(sIO, ~ Ns(DMdur, knots=c(0,1,3,6,10)), from = "DM")
NOTE:
Multiple transitions *from* state ' DM ' - are you sure?
The analysis requested is effectively merging outcome states.
You may want analyses using a *stacked* dataset - see ?stack.Lexis
stats::glm Poisson analysis of Lexis object sIO with log link:
Rates for transitions:
DM->Dead
DM->OAD
DM->Ins
> round(ci.exp(mDM), 3)
                                    exp(Est.)  2.5% 97.5%
(Intercept)                             0.722 0.693 0.753
Ns(DMdur, knots = c(0, 1, 3, 6, 10))1     0.297 0.256 0.346
Ns(DMdur, knots = c(0, 1, 3, 6, 10))2     0.247 0.208 0.293
Ns(DMdur, knots = c(0, 1, 3, 6, 10))3     0.013 0.010 0.015
Ns(DMdur, knots = c(0, 1, 3, 6, 10))4     0.553 0.479 0.640
```

The model is meaningless, not **statistically** meaningless, but **substantially** meaningless —not sensible to have same duration (or other) effect for different event types

Material

- Book on line: Practical Multistate Modeling
  https://bendixcarstensen.com/PMM/
- Book: Bendix Carstensen:
  Epidemiology with R, Oxford University Press, 2022
- Vignette in the Epi package:
  Analysis of follow-up data using the Lexis functions in Epi