Representation and prediction in multistate models

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Representation of FU

- Many different ways of representing follow-up:
  - msm
  - mstate
  - etm
- some dedicated to a special model
- mostly on one timescale (the st machinery in Stata)
- generally derived from follow-up in a clinical trial with
  - entry at 0
  - exit at t
  - risk time t

MSM representation

Epochs (time-intervals)

- **Time** at start: The value of the timescale**s** of interest.
- **Length** of the epoch — risk time ("exposure")
- **State** in which the the time is spent
- **next** state: the state the person moves on to

This is a representation of the **risk time**

Representation of likelihood

- The likelihood terms in a multistate model comes naturally as one per **transition**:
- $$\exp\left(\int_{\text{in}}^{\text{out}} \lambda_j(u)\,\mathrm{d}u\right)$$
- . . . and for the events, additionally $\lambda_j(\text{out})$
- This is the **stacked** representation, allowing joint modeling of all transition rates in one go:
- Separate or joint parameters for each transition.

Lexis objects

data.frame with a few extra features:
timescales — chose any number, name as you please
lex.id — person identification
lex.dur — length of the epoch represented
lex.Cst — state of risk time (Current state)
lex.Xst — neXt state

Lexis objects - split objects

Splitting time with splitLexis:

- risk time in many small intervals
- assuming constant rates in each
- allows simple parametric modeling with glm
- using any number of time scales
- prediction of rates
- calculation of any derived measure

glm modeling form object Lx

```
> w2i <- glm( lex.Xst=="Ill" ~ v1 + v2 + v3,
+             family=poisson, offset=log(lex.dur),
+             data = subset( Lx, lex.Cst=="Well" ) )
> #
> w2d <- glm( lex.Xst=="Dead" ~ v1 + v2 + v3,
+             family=poisson, offset=log(lex.dur),
+             data = subset( Lx, lex.Cst=="Well" ) )
> #
> i2d <- glm( lex.Xst=="Dead" ~ v1 + v2 + v3,
+             family=poisson, offset=log(lex.dur),
+             data = subset( Lx, lex.Cst=="Ill" ) )
```


coxph modeling form object Lx

```
> w2i <- coxph( Surv( time, time+lex.dur, lex.Xst=="Ill" ) ~ v1 + v2 + v3,
+               data = subset( Lx, lex.Cst=="Well" ) )
> #
> w2d <- coxph( Surv( time, time+lex.dur, lex.Xst=="Dead" ) ~ v1 + v2 + v3,
+               data = subset( Lx, lex.Cst=="Well" ) )
> #
> i2d <- coxph( Surv( time, time+lex.dur, lex.Xst=="Dead" ) ~ v1 + v2 + v3,
+               data = subset( Lx, lex.Cst=="Ill" ) )
```

glm modeling form object Lx with update

```
> w2i <- glm( lex.Xst=="Ill" ~ v1 + v2 + v3,
+             family=poisson, offset=log(lex.dur),
+             data = subset( Lx, lex.Cst=="Well" ) )
> #
> w2d <- update( w2i, lex.Xst=="Dead" ~ . )
> #
> i2d <- update( w2d, data = subset( Lx, lex.Cst=="Ill" ) )
```

— but if you really **are** using the same covariates:

```
> mA <- glm( lex.Fail ~ lex.Tr + (v1 + v2 + v3):lex.Tr,
+            family=poisson, offset=log(lex.dur),
+            data = stack.Lexis( Lx ) )
```

lex.Tr has levels "Well->Ill", "Well->Dead" and "Ill->Dead"

Stacking – interface to mstate

- Stacking of the follow-up gives the terms that make up the likelihood
- lex.Tr has levels "Well->Ill", "Well->Dead" and "Ill->Dead"
- lex.Fail is logical.
- Used for the interface function msdata.Lexis — stacks the data and shaves away features.

Utilities — summaries

- summary — gives table of transitions and risk time
- boxes — shows it in a nice transition diagram (boxes)
- plot — plots follow-up in a Lexis diagram

Utilities — manipulation & restructuring

- cutLexis — cuts follow-up at a time point; transition to a new state.
- splitLexis — splits time in small intervals along a time scale at designated breaks.
- Both features need stsplit in Stata (+plus a bit of fidgeting)

Predicting using a single time scale

- With a parametric model for rates:
- closed form expressions for state probabilities etc.
- wrapping in a function with parameters as arguments
- parametric bootstrap does all for you
- multistate machinery from Michael C

Prediction using realistic models

- Simulation of an entire dataset through MS model
  - allowing multiple time scale
  - . . . also "time since state S"
- Enumeration of persons in states gives
- — state occupancy probabilities
- — expected sojourn times
- — expected life time probabilities

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ARTICLE

Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial

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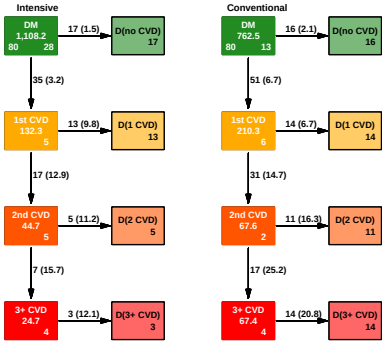
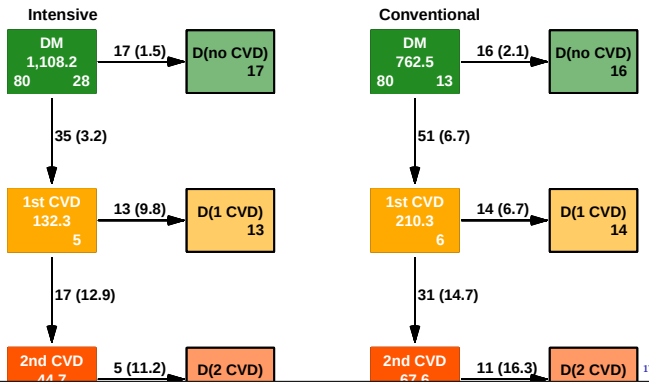
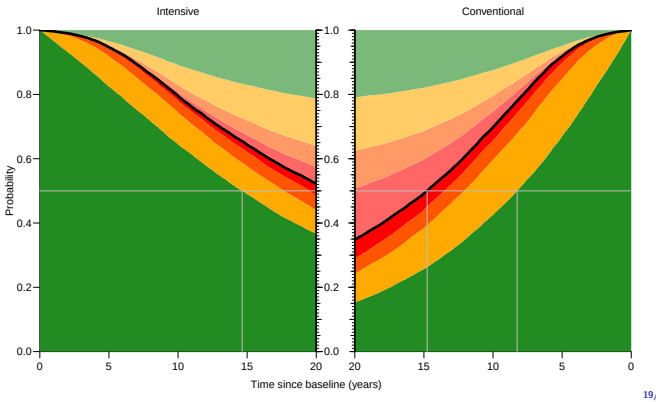
Abstract
Aims/hypothesis The aim of this work was to study the potential long-term impact of a 7.8 years intensified multifactorial pharmacological approaches. After 7.8 years the study continued as an observational follow-up with all patients receiving treatment as for the original intensive therapy group. The pri-

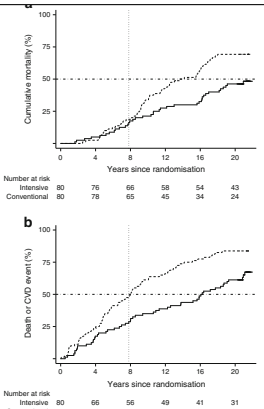




Hazard ratios

	CVD event	Mortality
HR, Int. vs. Conv.	0.55 (0.39;0.77)	0.83 (0.54; 1.30)
H_0: PH btw. CVD groups	p=0.438	p=0.261
H_0: HR = 1	p=0.425	p=0.001
HR vs. 0 CVD events:		
0 (ref.)	1.00	1.00
1	2.43 (1.67;3.52)	3.08 (1.82; 5.19)
2	3.48 (2.15;5.64)	4.42 (2.36; 8.29)
3+		7.76 (4.11;14.65)





between groups (HR 0.83 [95% CI 0.54, 1.30]; p=0.43). Thus, the reduced mortality was primarily due to reduced risk of CVD.

The patients in the intensive group experienced a total of 90 cardiovascular events vs 195 events in the conventional group. Nineteen intensive-group patients (24%) vs 34 conventional-group patients (43%) experienced more than one cardiovascular event. No significant between-group difference in the distribution of specific cardiovascular first-event types was observed (Table 2 and Fig. 4).

Microvascular complications Hazard rates of progression rates in microvascular complications compared with baseline status are shown Fig. 3. Sensitivity analyses showed a negligible effect of the random dates imputation.

Progression of retinopathy was decreased by 33% in the intensive-therapy group (Fig. 5). Blindness in at least one eye was reduced in the intensive-therapy group with an HR of 0.47 (95% CI 0.23, 0.98, p=0.044). Autonomic neuropathy was decreased by 41% in the intensive-therapy group (Fig. 5). We observed no difference between groups in the progression of peripheral neuropathy (Fig. 5). Progression to diabetic nephropathy (macroalbuminuria) was reduced by 48% in the intensive-therapy group (Fig. 5). Ten patients in the conventional-therapy groups vs five patients in the intensive-therapy group progressed to end-stage renal disease (p=0.061).

Discussion

Expected lifetime and YLL (well, gained)

Expected lifetime (years) in the Steno 2 cohort during the first 20 years after baseline by treatment group and CVD status.

State	Intensive	Conventional	Int.−Conv.
Alive	15.6	14.1	1.5
No CVD	12.7	10.0	2.6
Any CVD	3.0	4.1	−1.1

Expected lifetime (years) during the first 20 years after baseline by sex, age, treatment group and CVD status.

sex		Men			Women		
state	age	Int.	Conv.	Int.−Conv.	Int.	Conv.	Int.−Conv.
Alive	45	18.5	17.5	1.0	19.1	18.4	0.7
	50	17.2	16.1	1.1	18.0	17.2	0.8
	55	15.6	13.8	1.8	17.4	15.9	1.6
	60	13.9	11.6	2.2	15.5	13.7	1.8
	65	11.2	9.5	1.8	13.3	11.4	2.0
No CVD	45	14.9	12.5	2.4	15.8	14.3	1.5
	50	14.0	11.1	2.9	15.1	12.9	2.2
	55	12.2	9.7	2.5	14.3	11.6	2.7
	60	10.9	8.2	2.7	12.4	9.9	2.6
	65	9.0	6.7	2.2	10.7	8.3	2.4

Multistate models in practice:

- Representation:
  - States
  - Transitions
  - Sojourn times
  - Rates
- Analysis of rates:
  - Cox-model
  - Poisson model
- Reporting
  - Rates
  - HRs
  - Probabilities
  - Expected lifetime

Representation of multistate FU: Lexis

- Allowing multiple time scales
  - time-scale variables — the starting point on each time scale
  - sojourn time variable `lex.dur` — risktime, exposure
  - state variables:
- Allowing multiple states
  - `lex.Cst` — the state in which follow-up (`lex.dur`) occurs
  - `lex.Xst` — the state in which

```
> head( st2[,-c(1,4:5,12,13)] )

    allocation sex    doBth     doDM   doBase   doCVD1   doCVD2   doCVD3    doDth
1    Intensive   M 1932.300 1991.093 1993.357 2014.457       NA       NA       NA
2    Intensive   M 1946.813 1982.130 1993.357 2009.231 2009.570 2010.162       NA
3 Conventional   M 1943.377 1982.560 1993.362 2001.639       NA       NA 2001.639
4 Conventional   M 1944.771 1976.791 1993.362 1995.415 1997.461 2003.443 2003.443
5 Conventional   M 1935.993 1986.346 1993.162 1993.959 1994.657 1998.047 1998.047
6 Conventional   M 1946.942 1986.404 1993.201 1998.769       NA       NA       NA
```



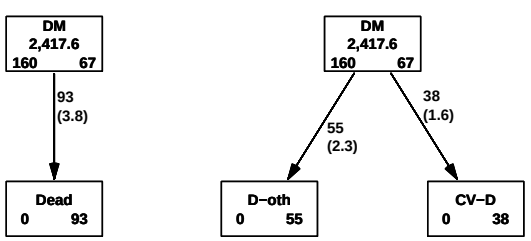
```
> L2 <- Lexis( entry = list( per = doBase,
+                            age = doBase-doBth,
+                            dur = doBase-doDM,
+                            tsb = 0 ),
+              exit = list( per = doEnd ),
+              exit.status = factor( ( !is.na(doDth) ) + deathCVD,
+                                    labels=c("DM","D-oth","CV-D") ),
+              data = st2 )

NOTE: entry.status has been set to "DM" for all.

> summary( L2 )

Transitions:
     To
From DM D-oth CV-D  Records:  Events: Risk time:  Persons:
  DM 67    55   38       160       93     2417.6       160
```



```
> L0 <- Lexis( entry = list( per = doBase,
+                            age = doBase-doBth,
+                            dur = doBase-doDM,
+                            tsb = 0 ),
+              exit = list( per = doEnd ),
+              exit.status = factor( ( !is.na(doDth) ),
+                                    labels=c("DM","Dead") ),
+              data = st2 )

NOTE: entry.status has been set to "DM" for all.

> summary( L0 )

Transitions:
     To
From DM Dead  Records:  Events: Risk time:  Persons:
  DM 67   93       160       93     2417.6       160
```



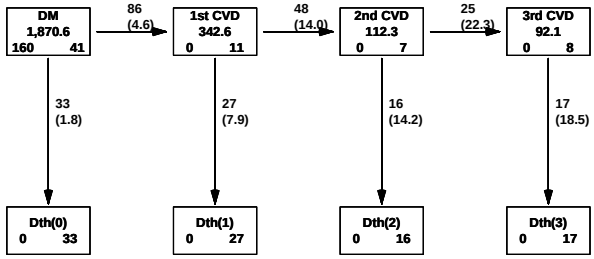
```
> par( mfrow=c(1,2) )
> boxes( L0, boxpos=list(x=c(50,50),y=c(85,15)),show.BE=T,scale.R=100)
> boxes( L2, boxpos=list(x=c(50,15,85),y=c(85,15,15)),show.BE=T,scale.R=100)
```

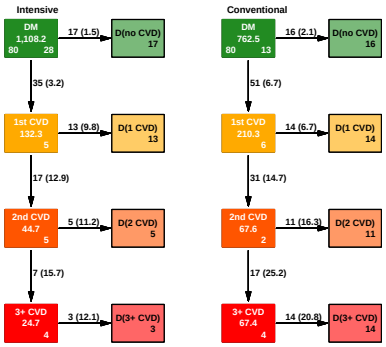



```
> L1 <- cutLexis( L0, cut = L0$doCVD1,
+                 new.state = "1st CVD",
+           precursor.states = c("DM"),
+               split.states = TRUE,
+                  new.scale = "tfCVD")
> #
> L1 <- cutLexis( L1, cut = L1$doCVD2,
+                 new.state = "2nd CVD",
+           precursor.states = c("DM","1st CVD"),
+               split.states = TRUE )
> #
> L1 <- cutLexis( L1, cut = L1$doCVD3,
+                 new.state = "3rd CVD",
+           precursor.states = c("DM","1st CVD","2nd CVD"),
+               split.states = TRUE )
> levels( L1 )

[1] "DM"                          "1st CVD"
[3] "2nd CVD"                     "3rd CVD"
[5] "Dead"                        "Dead(1st CVD)"
[7] "Dead(1st CVD)(2nd CVD)"      "Dead(1st CVD)(2nd CVD)(3rd CVD)"

> levels( L1$lex.Cst )[5:8] <-
+ levels( L1$lex.Xst )[5:8] <- paste("Dth(",0:3,")",sep="")
```



```
> boxes( L1, boxpos=list( x=c(rep(seq(15,85,,4),2) ),
+                         y=rep(c(85,20),each=4) ), show.BE=TRUE, scale.R=100 )
```





An added time scale

We added the timescale `tfCVD` using `new.scale="tfCVD"`

```
> subset( L1, lex.id==5 )[,1:9]

        per      age      dur       tsb    tfCVD   lex.dur lex.Cst lex.Xst lex.id
10 1993.162 57.16906 6.815916 0.0000000       NA 0.7967146      DM 1st CVD      5
11 1993.959 57.96578 7.612631 0.7967146 0.000000 0.6981520 1st CVD 2nd CVD      5
12 1994.657 58.66393 8.310783 1.4948665 0.698152 3.3894593 2nd CVD  Dth(2)      5
```

An added time scale I

We added the timescale `tfCVD` using `new.scale="tfCVD"`

```
> S1 <- splitLexis( L1, breaks=seq(0,25,1/12), time.scale="tsb" )
> subset( S1, lex.id==5 )[,1:9]
```

```
    lex.id      per      age      dur        tsb      tfCVD    lex.dur lex.Cst le
741      5 1993.162 57.16906 6.815916 0.00000000         NA 0.08333333      DM
742      5 1993.246 57.25240 6.899250 0.08333333         NA 0.08333333      DM
743      5 1993.329 57.33573 6.982583 0.16666667         NA 0.08333333      DM
744      5 1993.412 57.41906 7.065916 0.25000000         NA 0.08333333      DM
745      5 1993.496 57.50240 7.149250 0.33333333         NA 0.08333333      DM
746      5 1993.579 57.58573 7.232583 0.41666667         NA 0.08333333      DM
747      5 1993.662 57.66906 7.315916 0.50000000         NA 0.08333333      DM
748      5 1993.746 57.75240 7.399250 0.58333333         NA 0.08333333      DM
749      5 1993.829 57.83573 7.482583 0.66666667         NA 0.08333333      DM
750      5 1993.912 57.91906 7.565916 0.75000000         NA 0.04671458      DM 1s
751      5 1993.959 57.96578 7.612631 0.79671458 0.00000000 0.03661875 1st CVD 1s
752      5 1993.996 58.00240 7.649250 0.83333333 0.03661875 0.08333333 1st CVD 1s
```


An added time scale II

```
753      5 1994.079 58.08573 7.732583 0.91666667 0.11995209 0.08333333 1st CVD 1s
754      5 1994.162 58.16906 7.815916 1.00000000 0.20328542 0.08333333 1st CVD 1s
755      5 1994.246 58.25240 7.899250 1.08333333 0.28661875 0.08333333 1st CVD 1s
756      5 1994.329 58.33573 7.982583 1.16666667 0.36995209 0.08333333 1st CVD 1s
757      5 1994.412 58.41906 8.065916 1.25000000 0.45328542 0.08333333 1st CVD 1s
758      5 1994.496 58.50240 8.149250 1.33333333 0.53661875 0.08333333 1st CVD 1s
759      5 1994.579 58.58573 8.232583 1.41666667 0.61995209 0.07819986 1st CVD 2n
760      5 1994.657 58.66393 8.310783 1.49486653 0.69815195 0.00513347 2nd CVD 2n
761      5 1994.662 58.66906 8.315916 1.50000000 0.70328542 0.08333333 2nd CVD 2n
762      5 1994.746 58.75240 8.399250 1.58333333 0.78661875 0.08333333 2nd CVD 2n
763      5 1994.829 58.83573 8.482583 1.66666667 0.86995209 0.08333333 2nd CVD 2n
764      5 1994.912 58.91906 8.565916 1.75000000 0.95328542 0.08333333 2nd CVD 2n
765      5 1994.996 59.00240 8.649250 1.83333333 1.03661875 0.08333333 2nd CVD 2n
766      5 1995.079 59.08573 8.732583 1.91666667 1.11995209 0.08333333 2nd CVD 2n
767      5 1995.162 59.16906 8.815916 2.00000000 1.20328542 0.08333333 2nd CVD 2n
768      5 1995.246 59.25240 8.899250 2.08333333 1.28661875 0.08333333 2nd CVD 2n
769      5 1995.329 59.33573 8.982583 2.16666667 1.36995209 0.08333333 2nd CVD 2n
770      5 1995.412 59.41906 9.065916 2.25000000 1.45328542 0.08333333 2nd CVD 2n
771      5 1995.496 59.50240 9.149250 2.33333333 1.53661875 0.08333333 2nd CVD 2n
```


An added time scale III

```
772      5 1995.579 59.58573 9.232583 2.41666667 1.61995209 0.08333333 2nd CVD 2n
773      5 1995.662 59.66906 9.315916 2.50000000 1.70328542 0.08333333 2nd CVD 2n
774      5 1995.746 59.75240 9.399250 2.58333333 1.78661875 0.08333333 2nd CVD 2n
775      5 1995.829 59.83573 9.482583 2.66666667 1.86995209 0.08333333 2nd CVD 2n
776      5 1995.912 59.91906 9.565916 2.75000000 1.95328542 0.08333333 2nd CVD 2n
777      5 1995.996 60.00240 9.649250 2.83333333 2.03661875 0.08333333 2nd CVD 2n
778      5 1996.079 60.08573 9.732583 2.91666667 2.11995209 0.08333333 2nd CVD 2n
779      5 1996.162 60.16906 9.815916 3.00000000 2.20328542 0.08333333 2nd CVD 2n
780      5 1996.246 60.25240 9.899250 3.08333333 2.28661875 0.08333333 2nd CVD 2n
781      5 1996.329 60.33573 9.982583 3.16666667 2.36995209 0.08333333 2nd CVD 2n
782      5 1996.412 60.41906 10.065916 3.25000000 2.45328542 0.08333333 2nd CVD 2n
783      5 1996.496 60.50240 10.149250 3.33333333 2.53661875 0.08333333 2nd CVD 2n
784      5 1996.579 60.58573 10.232583 3.41666667 2.61995209 0.08333333 2nd CVD 2n
785      5 1996.662 60.66906 10.315916 3.50000000 2.70328542 0.08333333 2nd CVD 2n
786      5 1996.746 60.75240 10.399250 3.58333333 2.78661875 0.08333333 2nd CVD 2n
787      5 1996.829 60.83573 10.482583 3.66666667 2.86995209 0.08333333 2nd CVD 2n
788      5 1996.912 60.91906 10.565916 3.75000000 2.95328542 0.08333333 2nd CVD 2n
789      5 1996.996 61.00240 10.649250 3.83333333 3.03661875 0.08333333 2nd CVD 2n
790      5 1997.079 61.08573 10.732583 3.91666667 3.11995209 0.08333333 2nd CVD 2n
```


An added time scale IV

```
791      5 1997.162 61.16906 10.815916 4.00000000 3.20328542 0.08333333 2nd CVD 2n
792      5 1997.246 61.25240 10.899250 4.08333333 3.28661875 0.08333333 2nd CVD 2n
793      5 1997.329 61.33573 10.982583 4.16666667 3.36995209 0.08333333 2nd CVD 2n
794      5 1997.412 61.41906 11.065916 4.25000000 3.45328542 0.08333333 2nd CVD 2n
795      5 1997.496 61.50240 11.149250 4.33333333 3.53661875 0.08333333 2nd CVD 2n
796      5 1997.579 61.58573 11.232583 4.41666667 3.61995209 0.08333333 2nd CVD 2n
797      5 1997.662 61.66906 11.315916 4.50000000 3.70328542 0.08333333 2nd CVD 2n
798      5 1997.746 61.75240 11.399250 4.58333333 3.78661875 0.08333333 2nd CVD 2n
799      5 1997.829 61.83573 11.482583 4.66666667 3.86995209 0.08333333 2nd CVD 2n
800      5 1997.912 61.91906 11.565916 4.75000000 3.95328542 0.08333333 2nd CVD 2n
801      5 1997.996 62.00240 11.649250 4.83333333 4.03661875 0.05099247 2nd CVD  1
```


Representation of multistate FU: `Lexis` I

```
lex.id      per      age      dur      tsb    tfCVD   lex.dur lex.Cst lex.Xst
     5 1993.162 57.16906  6.815916 0.000000       NA 0.0833333      DM      DM
     5 1993.246 57.25240  6.899250 0.083333       NA 0.0833333      DM      DM
...
     5 1993.912 57.91906  7.565916 0.750000       NA 0.0467145      DM 1st CVD
     5 1993.959 57.96578  7.612631 0.796714 0.000000 0.0366187 1st CVD 1st CVD
     5 1993.996 58.00240  7.649250 0.833333 0.036618 0.0833333 1st CVD 1st CVD
...
     5 1994.579 58.58573  8.232583 1.416666 0.619952 0.0781998 1st CVD 2nd CVD
     5 1994.657 58.66393  8.310783 1.494866 0.698151 0.0051334 2nd CVD 2nd CVD
...
     5 1997.912 61.91906 11.565916 4.750000 3.953285 0.0833333 2nd CVD 2nd CVD
     5 1997.996 62.00240 11.649250 4.833333 4.036618 0.0509924 2nd CVD  Dth(2)
```


Modeling mortality rates in `Lexis` objects

```
> dlev <- c("D(no CVD)", "D(1 CVD)",  "D(2 CVD)",  "D(3+ CVD)")
> #
> m0 <- glm( (lex.Xst %in% dlev ) ~
+            Ns( tsb, knots=d.kn ) + lex.Cst + allocation,
+            offset = log(lex.dur),
+            family = poisson,
+            data = S1 )
> #
> m1  <- update( m0, . ~ . + sex + age )                        # the real model
> #
> m1i <- update( m1, . ~ . - allocation + allocation:lex.Cst )
> #
> # Test interaction
> anova( m1i, m1, test="Chisq" )
```


Modeling CVD rates in `Lexis` objects

```
> clev <- c("1st CVD","2nd CVD","3+ CVD")
> #
> c0 <- glm( ( (lex.Xst %in% clev) & (lex.Cst!=lex.Xst) ) ~
+            Ns( tsb, knots=d.kn ) + lex.Cst + allocation,
+            offset = log(lex.dur),
+            family = poisson,
+            data = subset( S1, lex.Cst!="3+ CVD" ) )
> #
> c1  <- update( c0, . ~ . + sex + age )
> #
> c1i <- update( c1, . ~ . - allocation + allocation:lex.Cst )
> #
> c1p <- update( c1, . ~ . + allocation:tsb )
> #
> # Test interaction & PH
> anova( c1i, c1, c1p, test="Chisq" )
```

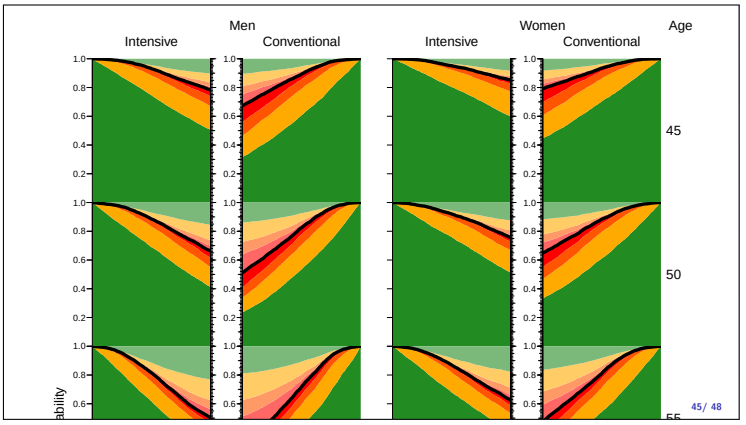

Simulation: transition object

```
> TM1 <- list( "DM" = list( "D(no CVD)" = m1,
+                           "1st CVD" = c1 ),
+         "1st CVD" = list(  "D(1 CVD)" = m1,
+                            "2nd CVD" = c1 ),
+         "2nd CVD" = list(  "D(2 CVD)" = m1,
+                            "3+ CVD" = c1 ),
+          "3+ CVD" = list( "D(3+ CVD)" = m1 ) )
```

Simulation: baseline (init) object

```
> St2 <- subset( L1, select = c(timeScales(L1),"lex.Cst","lex.dur",
+                               "allocation","sex") )
> levels(St2$lex.Cst) <- levels(S1$lex.Cst)
> nr <- nrow(St2)
> St2[1:nr,"tsb"] <- 0
> St2[1:nr,"lex.Cst"] <- levels(St2$lex.Cst)[1]
> St2[1:nr,"allocation"] <- levels(S1$allocation)[1]
> St2 <- rbind( St2, St2 )
> St2[1:nr,"allocation"] <- levels(S1$allocation)[2]
```

St2 is a copy of the original date with `allocation="Intensive"` plus a copy of the original date with `allocation="Conventional"`

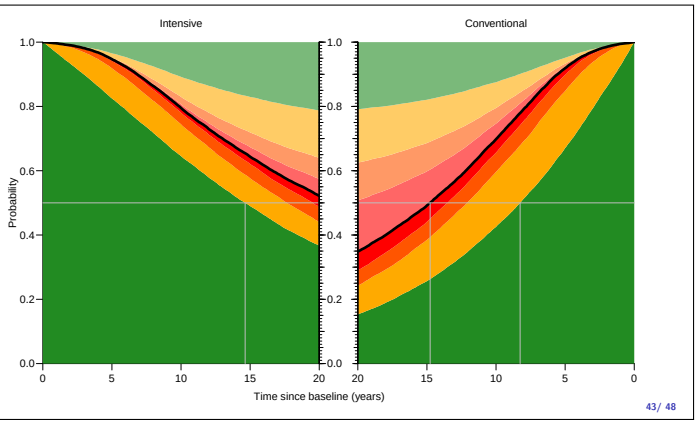


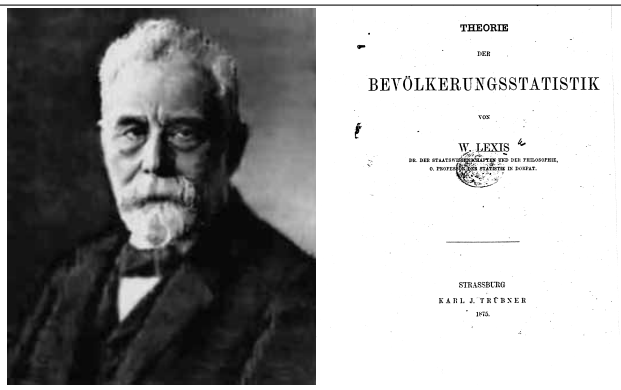
Simylating a follow up dataset

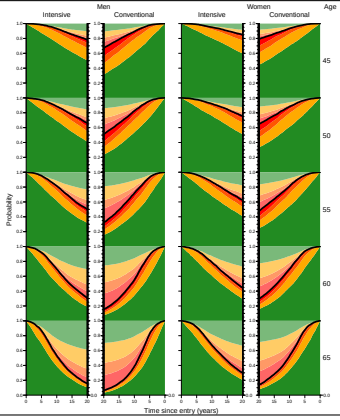
```
> sim2 <- simLexis( Tr = TM1,
+                   init = St2,
+                      N = 100,
+              time.pts = seq(0,21,0.1) )
> StC <- nState( subset(sim2,allocation=="Conventional"),
+                at=seq(0,20,0.1), from=0, time.scale="tsb" )
> StI <- nState( subset(sim2,allocation=="Intensive"),
+                at=seq(0,20,0.1), from=0, time.scale="tsb" )
> prm <- c(1:4,8:5)
> pC <- pState( StC, perm=prm )
> pI <- pState( StI, perm=prm )
```


History

- Epi package grew out of "Statistical Practice in Epidemiology with R", annually since 2002 in Tartu Estonia
- Lexis machinery conceived by Martyn Plummer, IARC
- Naming originally by David Clayton & Michael Hills, stlexis in Stata, later renamed stsplit
- David Claytion wrote a lexis function for the Epi package. Obsolete now.







Summary

- Proper representation of multistate data essential: States, transitions, risk time
- Readable modeling code
- Calculation of state probabilities requires a simulation in any realistic situation
- Examples of use in: http://bendixcarstensen.com/AdvCoh/Lexis-ex/

Thanks for your attention