Multistate models

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Common assumptions in survival analysis

1. Subjects are **either** “healthy” **or** “diseased”, with no intermediate state.
2. The disease is **irreversible**, or requires intervention to be cured.
3. The time of disease incidence is known **exactly**.
4. The disease is **accurately** diagnosed.

These assumptions are true for death and many chronic diseases.

Is the disease a dichotomy?

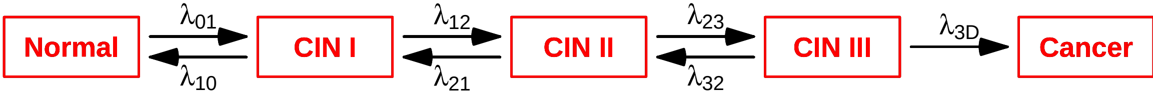
A disease may be preceded by a sub-clinical phase before it shows symptoms.

AIDS	Decline in CD4 count
Cancer	Pre-cancerous lesions
Type 2 Diabetes	Impaired glucose tolerance

Or a disease may be classified into degrees of severity (mild, moderate, severe).

A model for cervical cancer

Invasive squamous cell cancer of the cervix is preceded by cervical intraepithelial neoplasia (CIN)



The purpose of a screening programme is to detect and treat CIN.

Aim of the modeling the transition rates between states, is to be able predict how population moves between states

Probabilities of state occupancy can be calculated.

When does the disease occur?

You may need a clinical visit to diagnose the disease:

- examination by physician, or
- laboratory test on blood sample, or
- examination of biopsy by pathologist

We do not know what happens between consecutive visits (interval censoring).

Informative observation process?

Is the **reason** for the visit dependent on the **evolution** of disease?

Ignoring this may cause bias, like informative censoring.

Different reasons for follow-up visits:

- Fixed intervals (OK)
- Random intervals (OK)
- Doctor's care (OK)
- Self selection (**Not** OK — visits are likely to be close to event times)

Markov models for multistate diseases

The natural generalization of Poisson regression to multiple disease states:

- Probability of transition between states depends **only** on current state
- — this is the **Markov** property
- ⇒ transition rates are constant over time
- (time-fixed) covariates may influence transition rates
- the formal Markov property is **very** restrictive
- In clinical litterature "Markov model" is often used about any type of multistate model

Compnents of a multistate (Markov) model

- Define the disease states.
- Define which transitions between states are allowed.
- Select covariates influencing transition rates (may be different between transitions)
- Constrain some covariate effects to be the same, or zero.
- Not a trivial task — do we want *e.g.*
    - cause of death
    - disease status at death

Likelihood for multistate model

- The likelihood of the model depends on the probability of being in state j at time t_1, given that you were in state i at time t_0.
- Assume transition rates constant in small time intervals
- $\Rightarrow$ each interval contributes terms to the likelihood:
  - one for each person at risk of a transition in the interval
  - . . . for each possible transition
  - each term has the form of a Poisson likelihood contribution
  - the total likelihood for each time interval is a product of terms over persons and (possible) transitions
- Total likelihood is product of terms for all intervals
- — components **not** independent, but the total likelihood is a product; hence of the same form as the likelihood of independent Poisson variates

Purpose of multistate modeling

- Separation of intensities of interest (model definition)
- Evaluation of covariate effects on these
- — biological interpretability of covariate effects
- Use a fitted model to compute:
- state occupancy probabilities: $\mathrm{P}\left\{\text{in state } X \text{ at time } t\right\}$
- time spent in a given state

Special multistate models

- If all transition rates depend on only one time scale
- — but possibly different (time-fixed) covariates
- ⇒ easy to compute state probabilities
- For this reason the most commonly available models
- but not the most realistic models.
- Realistically transition rates depend on:
- multiple time scales
- time since entry to certain states.

Multistate models with Lexis

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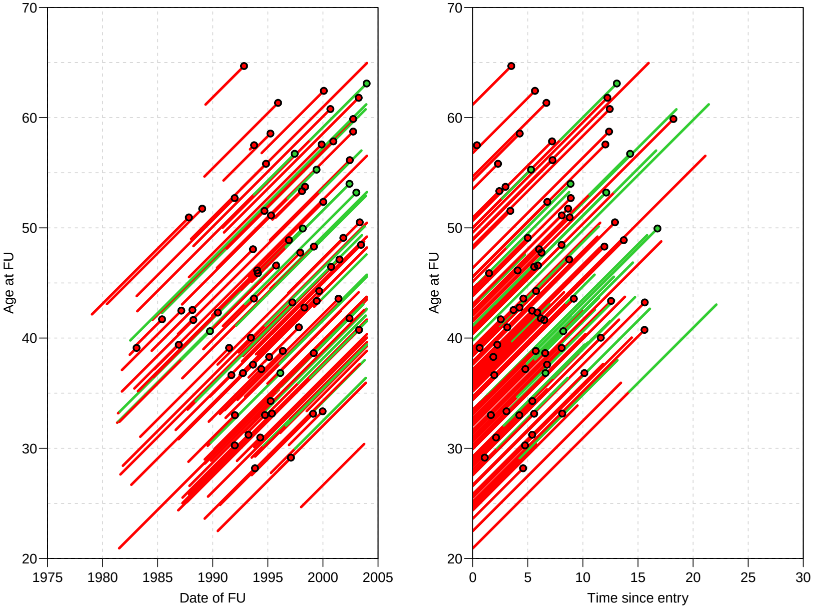
Example: Renal failure data from Steno

Hovind P, Tarnow L, Rossing P, Carstensen B, and Parving H-H: Improved survival in patients obtaining remission of nephrotic range albuminuria in diabetic nephropathy. *Kidney Int.*, 66(3):1180–1186, 2004.

- 96 patients entering at nephrotic range albuminuria (NRA), i.e. U-alb> 300mg/day.
- Is remission from this condition (i.e return to U-alb< 300mg/day) predictive of the prognosis?
- Endpoint of interest: Death or end stage renal disease (ESRD), i.e. dialysis or kidney transplant.

		Remission	
	Total	Yes	No
No. patients	125	32	93
No. events	77	8	69
Follow-up time (years)	1084.7	259.9	824.8
Cox-model:			
Timescale:	Time since nephrotic range albuminuria (NRA)		
Entry:	2.5 years of GFR-measurements after NRA		
Outcome:	ESRD or Death		
Estimates:	RR	95% c.i.	p
Fixed covariates:			
Sex (F vs. M):	0.92	(0.53,1.57)	0.740
Age at NRA (per 10 years):	1.42	(1.08,1.87)	0.011
Time-dependent covariate:			
Obtained remission:	0.28	(0.13,0.59)	0.001


Age at FU
70
60
50
40
30
20
1975
1980
1985
1990
1995
2000
2005
Date of FU
Age at FU
70
60
50
40
30
20
0
5
10
15
20
25
30
Time since entry

Features of the analysis

- Remission is included as a time-dependent variable.
- Age at entry is included as a fixed variable.

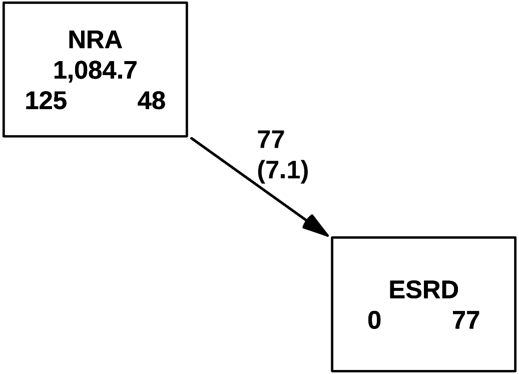
```
renal[1:5,]
id      dob      doe      dor      dox event
17 1967.944 1996.013       NA 1997.094     2
26 1959.306 1989.535 1989.814 1996.136     1
27 1962.014 1987.846       NA 1993.239     3
33 1950.747 1995.243 1995.717 2003.993     0
42 1961.296 1987.884 1996.650 2003.955     0
```

Note patient 26, 33 and 42 obtain remission.

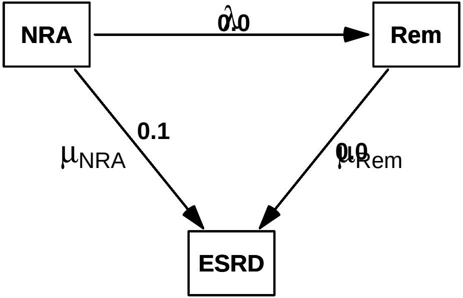
```
> Lr <- Lexis( entry = list( per=doe,
+                            age=doe-dob,
+                            tfi=0 ),
+               exit = list( per=dox ),
+        exit.status = event>0,
+             states = c("NRA","ESRD"),
+               data = renal )
> summary( Lr )

Transitions:
     To
From   NRA ESRD  Records:  Events: Risk time:  Persons:
  NRA  48   77         125         77    1084.67        125
```

```
> boxes( Lr, boxpos=list(x=c(25,75),
+                        y=c(75,25)),
+              scale.R=100, show.BE=TRUE )
```



Illness-death model



λ: remission rate.

μ_{NRA}: mortality/ESRD rate **before** remission.

μ_{rem}: mortality/ESRD rate **after** remission.

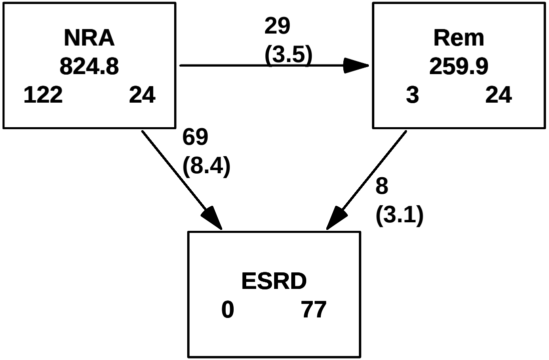
Cutting follow-up at remission: cutLexis

```
> Lc <- cutLexis( Lr, cut=Lr$dor,
+                timescale="per",
+                new.state="Rem",
+        precursor.states="NRA" )
> summary( Lc )

Transitions:
     To
From  NRA Rem ESRD  Records:  Events: Risk time:  Persons:
  NRA  24  29   69       122       98     824.77       122
  Rem   0  24    8        32        8     259.90        32
  Sum  24  53   77       154      106    1084.67       125
```

Showing states and FU: boxes.Lexis

```
> boxes( Lc, boxpos=list(x=c(15,85,50),
+                        y=c(85,85,20)),
                 scale.R=100, show.BE=TRUE )
```



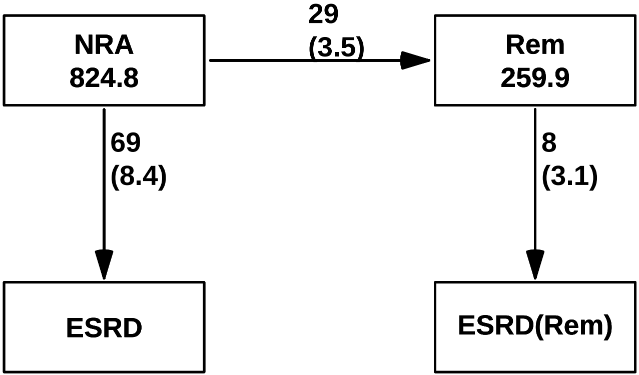
Splitting states: cutLexis

```
> Lc <- cutLexis( Lr, cut=Lr$dor,
+               timescale="per",
+               new.state="Rem",
+        precursor.states="NRA",
+            split.states=TRUE )
> summary( Lc )

Transitions:
     To
From  NRA Rem ESRD ESRD(Rem)  Records:  Events: Risk time:  Persons:
  NRA  24  29   69         0       122       98     824.77       122
  Rem   0  24    0         8        32        8     259.90        32
  Sum  24  53   69         8       154      106    1084.67       125
```

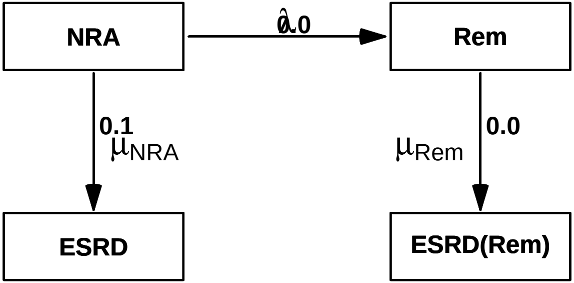
Showing states and FU: boxes.Lexis

```
> boxes( Lc, boxpos=list(x=c(15,85,15,85),
+                               y=c(85,85,20,20)), scale.R=100 )
```



Likelihood for a general MS-model

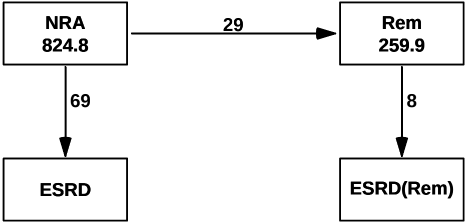
- Product of likelihoods for each transition
  — each one as for a survival model
- **Risk time** is the risk time in the “From” state
- **Events** are transitions to the “To” state
- All other transitions out of “From” are treated as **censorings**
- Possible to fit models separately for each transition



Cox-analysis with remission as time-dependent covariate:

- Ignores λ, the remission rate.
- Assumes μ_{NRA} and μ_{rem} use the same timescale.

Model for all transitions



Cox-model:

- Different timescales for transitions possible
- . . . only one per transition
- No explicit representation of estimated rates.

Poisson-model:

- Timescales can be different
- Multiple timescales can be accomodated simultaneously
- Explicit representation of all transition rates

Calculus of probabilities

$$\mathrm{P}\left\{\text{Remission } \textbf{before} \text{ time } t\right\}$$

$$= \int_0^t \lambda(u)\exp\left(-\int_0^u \lambda(s) + \mu_{\mathsf{NRA}}\,\mathrm{d}s\right)\,\mathrm{d}u$$

$$\mathrm{P}\left\{\text{Being in remission } \textbf{at} \text{ time } t\right\}$$

$$= \int_0^t \lambda(u)\exp\left(-\int_0^u \lambda(s) + \mu_{\mathsf{NRA}}(s)\,\mathrm{d}s\right) \times \exp\left(-\int_u^t \mu_{\mathsf{rem}}(s)\,\mathrm{d}s\right)\,\mathrm{d}u$$

Note μ_{rem} could also depend on u, time since obtained remission.

Sketch of programming, assuming that λ (lambda), μ_{NRA} (mu.nra) and μ_{rem} (mu.rem) are known for each age (stored in vectors)

```
c.rem      <- cumsum( lambda )
c.mort.nra <- cumsum( mu.nra )
c.mort.rem <- cumsum( mu.rem )
pr1  <- cumsum( lambda * exp( -( c.rem + c.mort.nra ) ) )

intgr(t,s) <- function(t,s){
           lambda[s] * exp( -( c.rem[s] + c.mort.nra[s] ) ) *
                    exp( -( c.mort.rem[t]-c.mort.rem[s] ) ) }
for( t in 1:100 ) p2[t] <- sum( intgr(t,1:t) )
```

If μ_{rem} depends on time of remission, then `c.mort.rem` should have an extra argument.

Calculation of integrals

The possibility of computing the state-occupancy probabilities relies on:

- Availablity of closed-form formulae for the probailities in terms of the transition rates
- Transition rates are assumed to be continuous functions of time
- Transition rates can be calulated at any point of time. . .
- This will allow simple calulation of the integrals from the closed-form expressions.

Semi-Markov models

- **if** we only have one time scale, which is common for **all** transitions
- — in practical terms: transition intensities only depend on state and the current time.
- then we can construct transition matrices for each tiny time interval

$$P_{ij}(t, t+h) = \mathrm{P}\left\{\text{state } j \text{ at } t+h \mid \text{state } i \text{ at } t\right\}$$

- Simple matrix multiplication then gives the matrix of transition probabilities between states between any two timepoints.

Prediction in multistate models: `simLexis` and renal failure

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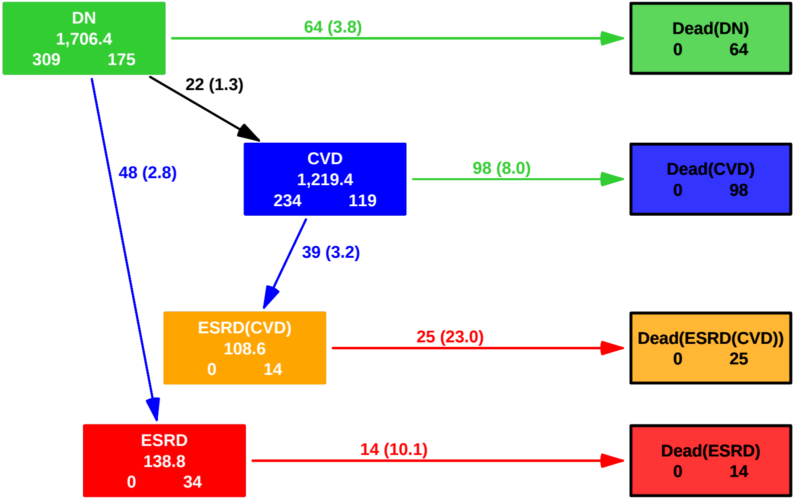
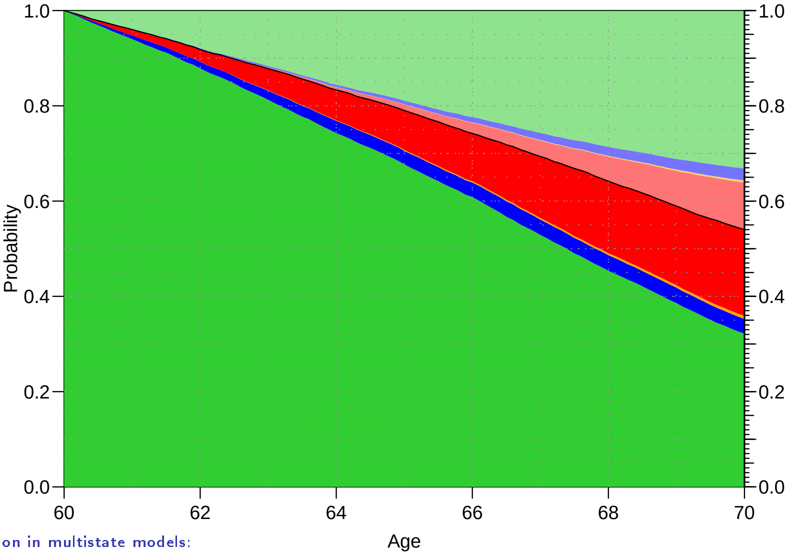
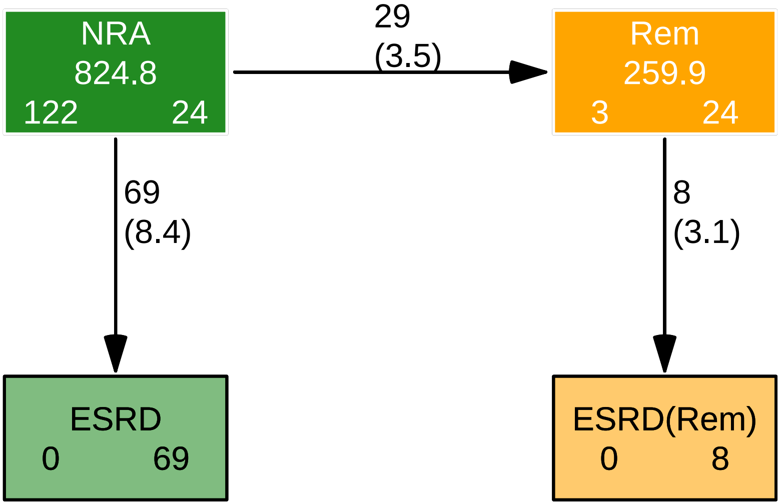
A more complicated multistate model



A more complicated multistate model




NRA
824.8
122
24
29
(3.5)
Rem
259.9
3
24
69
(8.4)
8
(3.1)
ESRD
0
69
ESRD(Rem)
0
8

Modeling in a multistate model

Each transition modeled by a model for rates
(Cox-model, Poisson-model for split data, glm or gam):

```
> sLc <- splitLexis( Lc, "tfi", breaks=seq(0,30,1/12) )
> # Rem-rate
> mr <- gam( cbind(lex.Xst=="Rem",lex.dur)
+            ~ s( tfi, k=10 ) + sex,
+            family = poisreg,
+              data = subset( sLc, lex.Cst=="NRA" ) )
> # ESRD-rates
> mx <- gam( cbind( lex.Xst %in% c("ESRD","ESRD(Ren)"), lex.dur )
+            ~ s(tfi,k=10) + sex + I((doe-dob-40)/10) + I(lex.Cst=="Rem"),
+            family = poisreg,
+              data = subset(sLc, lex.Cst %in% c("NRA","Rem")) )
```

. . . using the Lexis properties

```
> # Rem-rate
> mr <- gam.Lexis( sLc, from="NRA", to="Rem",
+                        formula = ~ s( tfi, k=10 ) + sex )

mgcv::gam Poisson analysis of Lexis object sLc with log link:
Rates for the transition:
NRA->Rem

> # ESRD-rates
> mx <- gam.Lexis( sLc, formula = ~ s(tfi,k=10) + sex +
+                        I((doe-dob-40)/10) + I(lex.Cst=="Rem") )

mgcv::gam Poisson analysis of Lexis object sLc with log link:
Rates for transitions:
NRA->ESRD
Rem->ESRD(Rem)
```

Default is to model all transitions

State probabilities

How do we get from rates (Poisson-models) to probabilities:

1. Analytic calculations:
   - immensely complicated formulae
   - computationally fast (once implemented)
   - difficult to generalize
2. Simulation of persons' histories
   - conceptually simple
   - computationally not quite simple
   - easy to generalize
   - hard to get confidence intervals (bootstrap)

Simulation of a survival time

- For a rate function $\lambda(t)$, $\Lambda(t) = \int_0^t \lambda(s)\,\mathrm{d}s$:

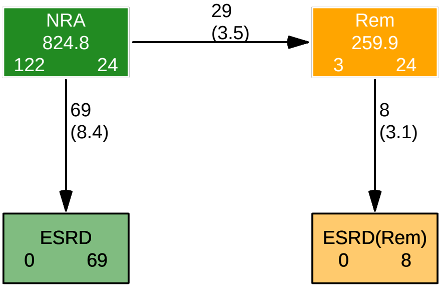
$$S(t) = \exp\bigl(-\Lambda(t)\bigr)$$

- Simulate a survival probability $u \in [0,1]$:

$$u = S(t) \quad \Leftrightarrow \quad \Lambda(t) = -\log(u)$$

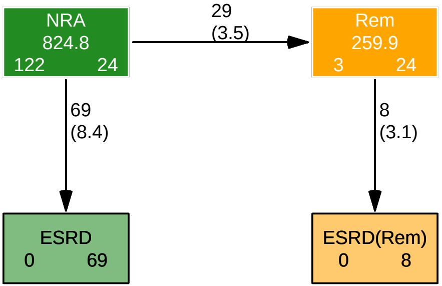
- Knowledge of $\Lambda(t)$ makes it easy to find a survival time — essentially just linear interpolation.

Simulation in a multistate model



- Simulate a "survival time" for each transition **out** of a state.
- The smallest of these is the transition time.
- Choose the corresponding transition type as transition.

Transition objects are glm/gam



```
> Tr <- list( "NRA" = list( "ESRD"      = mx,
+                           "Rem"       = mr ),
+             "Rem" = list( "ESRD(Rem)" = mx ) )
```

simLexis

Input required:

- A Lexis object representing the initial state of the persons to be simulated.
  (lex.dur and lex.Xst will be ignored.)
- A transition object with the estimated Poisson models collected in a list of lists.

Output produced:

- A Lexis object with simulated event histories for may persons
- Use nState to count how many persons in each state at different times

Using simLexis I

Put one record a new Lexis object (init, say). representing a person with the desired covariates.

Must have same structure as the one used for estimation — time scales must be initiated even if not used in models

```
> init <- sLc[NULL,c(timeScales(sLc),"lex.Cst")]
> init[1,"per"] <- 1994
> init[1,"age"] <- 40
> init[1,"tfi"] <- 0
> init[1,"lex.Cst"] <- "NRA"
> init[1,"sex"] <- "M"
> init[1,"dob"] <- 1954
> init[1,"doe"] <- 1994
> init
```

```
  per age tfi lex.Cst sex  dob  doe
 1994  40   0     NRA   M 1954 1994
```

Using simLexis II

```
> system.time(
+ sim1 <- simLexis( Tr, init, N=10000 ) )
```

```
   user  system elapsed
  23.89    1.30   25.19
```

```
> summary(sim1)
```

```
Transitions:
     To
From  NRA  Rem ESRD ESRD(Rem)  Records:   Events: Risk time:  Persons:
  NRA 270 1890 7840         0     10000      9730   74973.77     10000
  Rem   0  920    0       970      1890       970   20623.57      1890
  Sum 270 2810 7840       970     11890     10700   95597.33     10000
```

Using a simulated Lexis object — pState I

```
> NN <- nState( sim1, at = seq(0,15,0.1),
+                    from = 0,
+              time.scale = "tfi" )
> head( NN )

     State
when    NRA   Rem  ESRD ESRD(Rem)
  0   10000     0     0         0
  0.1  9949    30    21         0
  0.2  9888    63    49         0
  0.3  9835    84    81         0
  0.4  9785   112   103         0
  0.5  9752   129   119         0

> nw1 <- pState( NN, perm = c(1,2,4,3) )
> head( nw1, 3 )
```

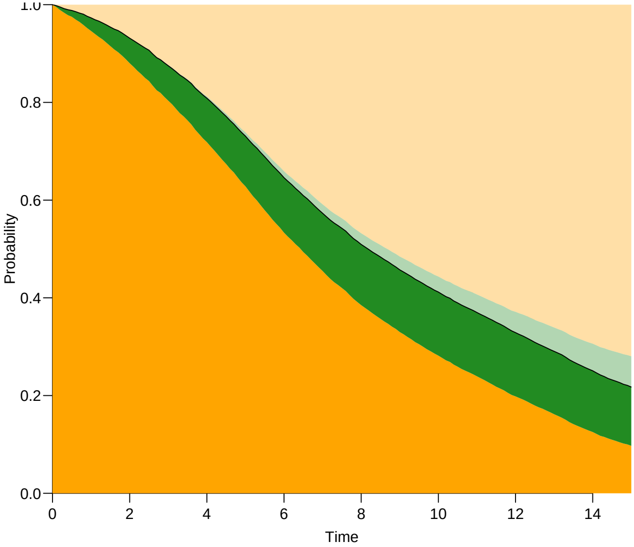
Using a simulated Lexis object — pState II

```
     State
when     NRA    Rem ESRD(Rem) ESRD
  0   1.0000 1.0000    1.0000    1
  0.1 0.9949 0.9979    0.9979    1
  0.2 0.9888 0.9951    0.9951    1
> tail( nw1, 3 )
      State
when      NRA    Rem ESRD(Rem) ESRD
  14.8 0.1018 0.2230    0.2846    1
  14.9 0.1000 0.2208    0.2829    1
  15   0.0971 0.2174    0.2804    1
> par( mar=c(3,3,0.1,0.1), mgp=c(3,1,0)/1.6, las=1 )
> plot( nw1, col=clr[c(2,1,4,3)] )
> lines( as.numeric(rownames(nw1)), nw1[,2] )
```

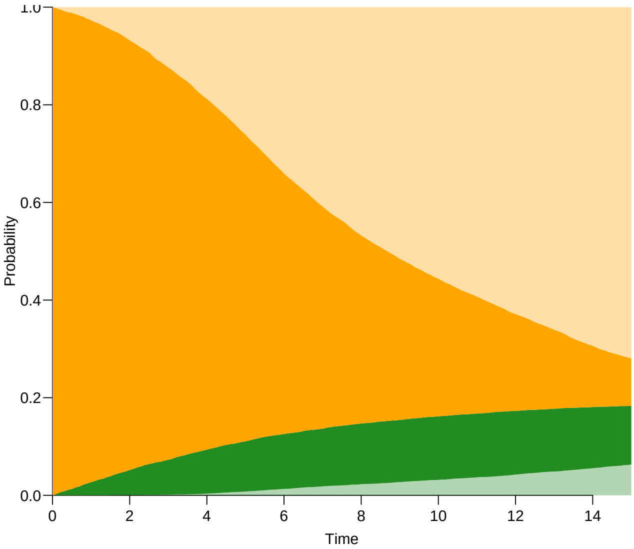
Using a simulated Lexis object — pState III

```
> nw2 <- pState( NN, perm = c(4,2,1,3) )
> head( nw2, 3 )

     State
when  ESRD(Rem)    Rem    NRA ESRD
  0            0 0.0000 1.0000    1
  0.1          0 0.0030 0.9979    1
  0.2          0 0.0063 0.9951    1

> tail( nw2, 3 )

      State
when   ESRD(Rem)    Rem    NRA ESRD
  14.8    0.0616 0.1828 0.2846    1
  14.9    0.0621 0.1829 0.2829    1
  15      0.0630 0.1833 0.2804    1

> par( mar=c(3,3,0.1,0.1), mgp=c(3,1,0)/1.6, las=1 )
> plot( nw2, col=clr[c(4,1,2,3)] )
```

Simulated probabilities



Simulated probabilities



How many persons should you simulate?

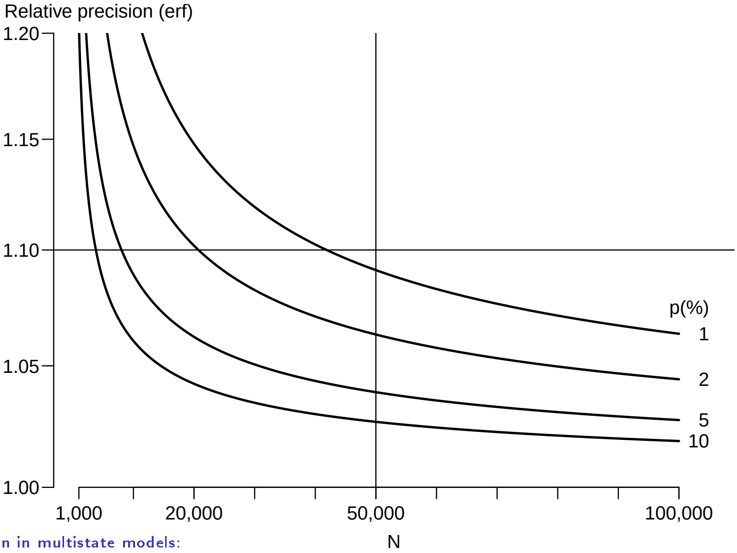
- All probabilities have the same denominator — the initial number of persons in the simulation, N, say.
- Thus, any probability will be of the form $p = x/N$
- For small probabilities we have that:

$$\text{s.e.}\big(\log(\hat{p})\big) = (1-p)/\sqrt{Np(1-p)}$$

- So c.i. of the form $p \overset{\times}{\div} \text{erf}$ where:

$$\text{erf} = \exp\big(1.96 \times (1-p)/\sqrt{Np(1-p)}\big)$$

Precision of simulated probabilities



Multistate model overview

- Clarify what the relevant states are
- Allows proper estimation of transition rates
- — and relationships between them
- Separate model for each transition (arrow)
- The usual survival methodology to compute probabilities breaks down
- Simulation allows estimation of cumulative probabilities:
    - Estimate transition rates (as usual)
    - Simulate probabilities (**not** as usual)