Multistate models

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Bendix Carstensen, Martyn Plummer

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A question of definition:
– consider occurrence of **recording of** a given disease

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- Transition rates between states
- Probability of state occupancy

Markov models for multistate processes

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- the formal Markov property is **very** restrictive
- in the clinical litterature "Markov model" is often used about any type of multistate model

Components of a multistate (Markov) model

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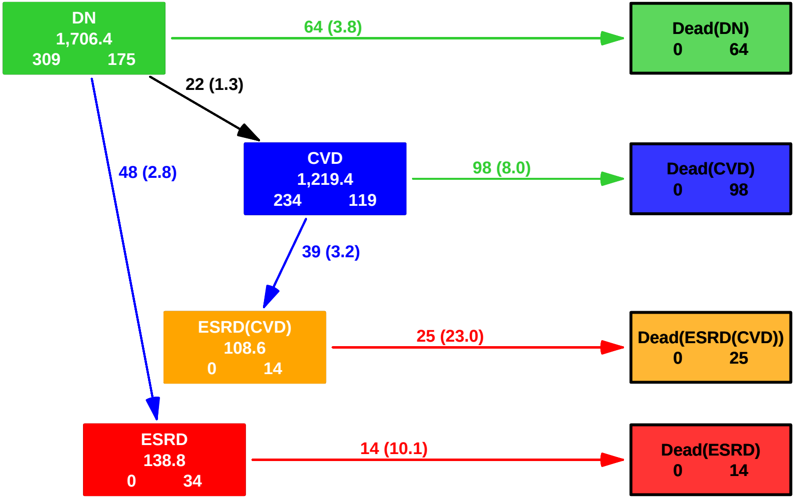
  - disease status at death (prev.CVD, prev.Can, neither)

A more complicated multistate model



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- terms are **not** independent, but the total likelihood is a product; hence of the same form as the likelihood from independent Poisson variates
- but observations from intervals from one person are neither Poisson nor independent

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No formulae means that any inference on state probabilities and sojourn times must be based on **simulation** from the model.

Multistate models with `Lexis`

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SPE, Tartu, Estonia,

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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.

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- Endpoint of interest: Death or end stage renal disease (ESRD), i.e. dialysis or kidney transplant.
- 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?

	Total	Remission Yes	Remission No
No. patients	125	32	93
No. events	77	8	69
Follow-up time (years)	1084.7	259.9	824.8

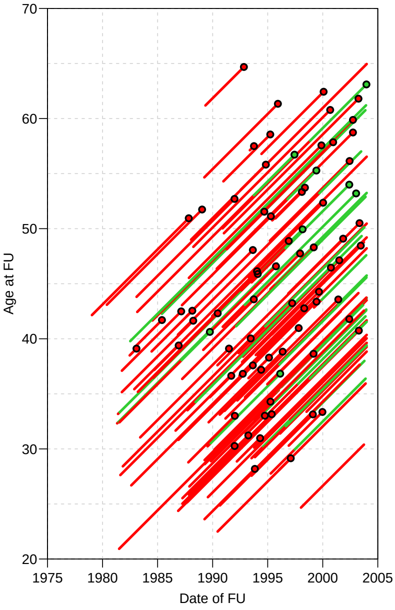
Cox-model:

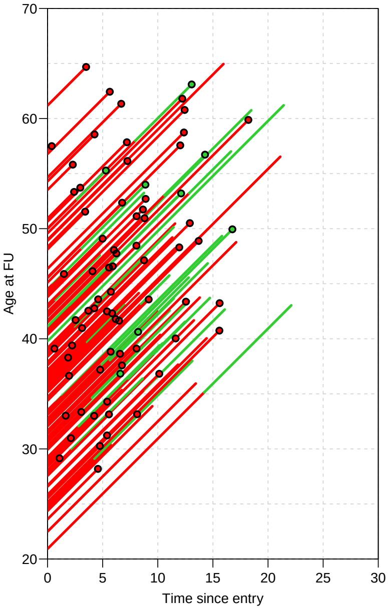
Timescale: Time since nephrotic range albuminuria (NRA)

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


70
60
50
40
30
20
1975
1980
1985
1990
1995
2000
2005
Date of FU
Age at FU


70
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50
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20
0
5
10
15
20
25
30
Time since entry
Age at FU

Features of the analysis

- Remission is included as a time-dependent 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.

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- Age at entry is included as a fixed variable.

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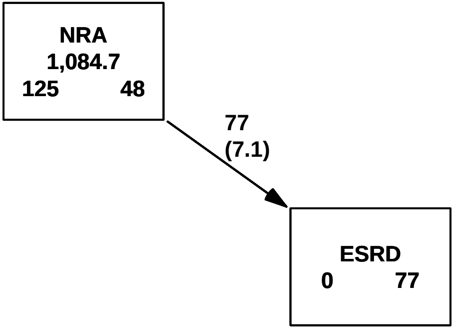
```

Note patient 26, 33 and 42 obtain remission.

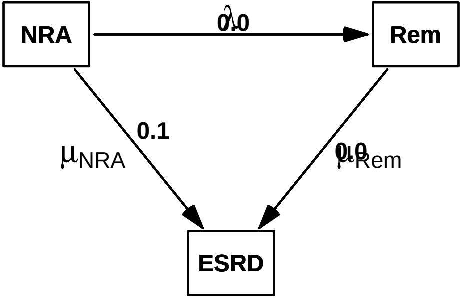
```
> Lr <- Lexis(entry = list(per = doe,
+                          age = doe-dob,
+                          tfi = 0),
+              exit = list(per = dox),
+       exit.status = event>0,
+            states = c("NRA", "ESRD"),
+              data = renal)
> summary(Lr)

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.

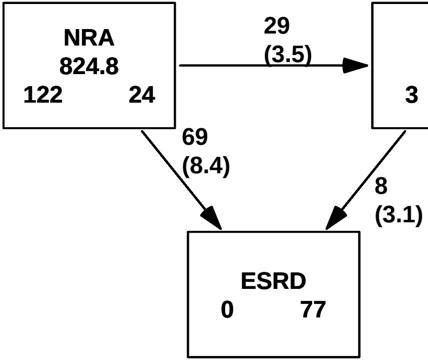
Cutting follow-up at remission: `cutLexis`

```
> 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)
```



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> boxes(Lc, boxpos = list(x = c(15, 85, 15, 85),
+                          y = c(85, 85, 20, 20)),
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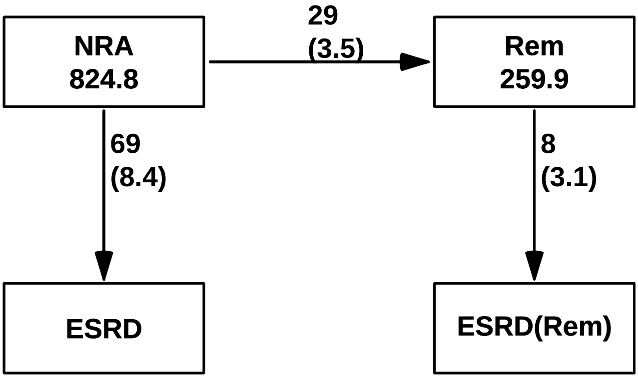

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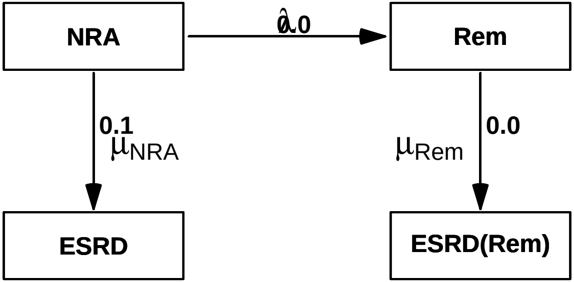
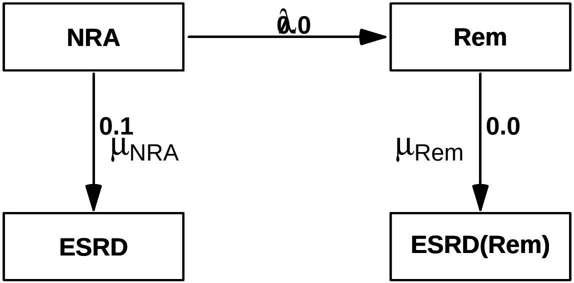
- **Risk time** is the risk time in the “From” state
- **Events** are transitions to the “To” state
- All other transitions out of “From” are treated as **censorings**
- Possible to fit models separately for each transition



Cox-analysis with remission as time-dependent covariate:

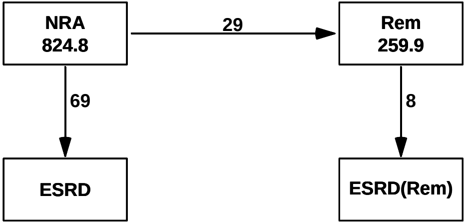
- Ignores λ, the remission rate.



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



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- Different timescales for transitions possible

Poisson-model:

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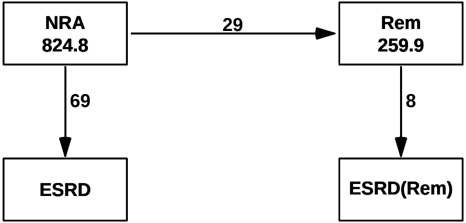

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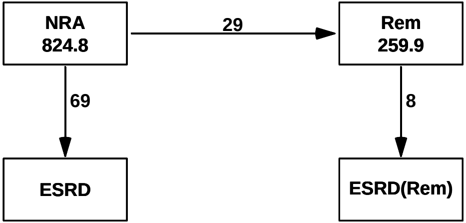

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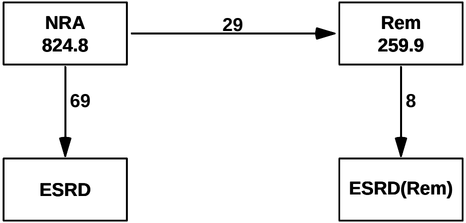

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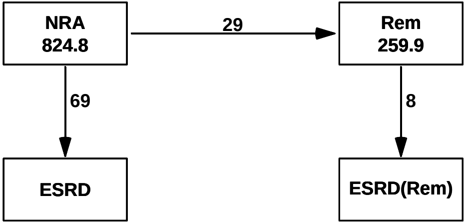

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Poisson-model:

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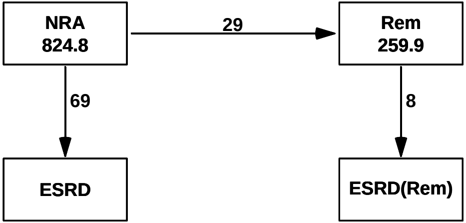
- Multiple timescales can be accomodated simultaneously

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

Calculating state 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 at any 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} also depends on time since remission, then `c.mort.rem` should have an extra argument—technically very complicated