Multi-state Models and the Survival package

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Changes

- survival 0.x: pre "white book": (1986 – 1989)
- survival 1.x: Splus era (1989 – 2004)
  - Second International S Conference, 1992, Toulouse
- survival 2.x: R (2004 – 2019)
- survival 3.x: on github 7/3, CRAN on 9/1?

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- Book: end of 2020

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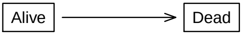
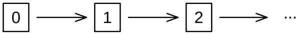
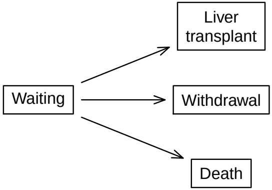
- 701 packages depend on `survival` (as of 4 July)

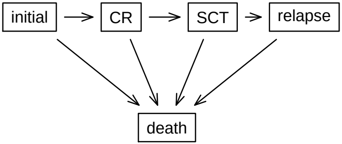
Why should you care?

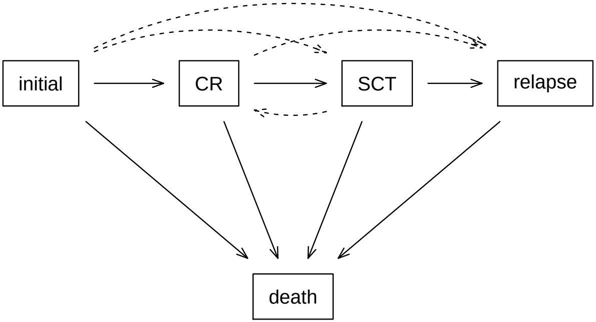
- I rarely change major versions – something must be up
- 701 packages depend on `survival` (as of 4 July)
- Major increments in multi-state modeling
- Why multi-state?


Alive
Dead


0
1
2
...


Waiting
Liver transplant
Withdrawal
Death


initial
CR
SCT
relapse
death


initial
CR
SCT
relapse
death

	id	trt	tstart	tstop	event
1	1	B	0	44	CR
2	1	B	44	113	relapse
3	1	B	113	235	death
4	2	A	0	200	SCT
5	2	A	200	286	death
6	3	A	0	38	CR
7	3	A	38	1983	censor

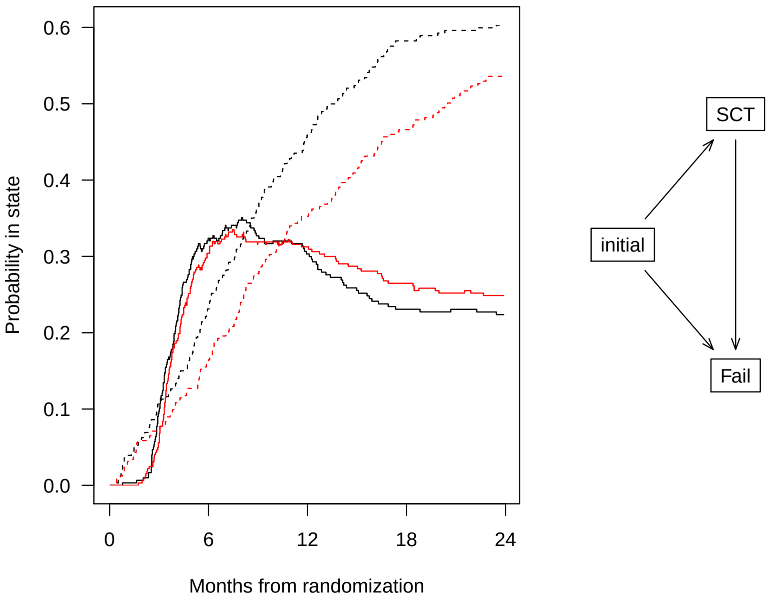
Data

- `event` is a multi-level factor variable.
  - The first level must correspond to "no event at this time"
  - Otherwise unrestricted.
- An `id` variable identifies multiple rows per subject.
- Consistent
  - If at risk, you should be some state: (0,50,T) (90, 210,M)
  - But only one place at a time: (0,50,T) (30, 210,P)

	id	trt	tstart	tstop	event	e2
1	1	B	0	44	CR	-
2	1	B	44	113	relapse	Fail
3	1	B	113	235	death	-
4	2	A	0	200	SCT	SCT
5	2	A	200	286	death	Fail
6	3	A	0	38	CR	-
7	3	A	38	1983	censor	-

```
> AJfit <- survfit(Surv(tstart, tstop, e2) ~ trt, id=id,
                  data=mydata, influence=TRUE)
> dim(AJfit)
strata states
     2      3
> print(AJfit, digits=2)
Call: survfit(formula = Surv(tstart, tstop, e2) ~ trt, data = my
    id = id, influence = TRUE)

                n nevent rmean std(rmean)*
trt=A, (s0) 759      0   527          47
trt=B, (s0) 821      0   651          49
trt=A, SCT  759    131   510          51
trt=B, SCT  821    134   569          52
trt=A, Fail 759    194  1382          59
trt=B, Fail 821    184  1198          58
   *mean time in state, restricted (max time = 2419 )
> plot(AJfit[, 2:3])
```


Probability in state
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
6
12
18
24
Months from randomization
SCT
initial
Fail

Multi-state coxph models

```
> cfit <- coxph(Surv(tstart, tstop, e2) ~ trt, id=id, mydata)
> print(cfit, digits=2)
Call:
coxph(formula = Surv(tstart, tstop, e2) ~ trt, data = mydata,
    id = id)


1:2     coef exp(coef) se(coef) robust se    z   p
  trtB -0.18      0.84     0.12      0.12 -1.4 0.2


1:3     coef exp(coef) se(coef) robust se    z    p
  trtB -0.24      0.79     0.13      0.13 -1.9 0.06


2:3     coef exp(coef) se(coef) robust se    z    p
  trtB -0.30      0.74     0.18      0.18 -1.7 0.08

 States:  1= (s0), 2= SCT, 3= Fail
```

Post coxph probability-in-state curves

```
> dummy <- data.frame(trt=c("A", "B"))
> csurv <- survfit(cfit, newdata=dummy)
> dim(csurv)
strata   data states
     1      2      3
> plot(csurv[,2:3], col=1:2, lty=c(1,1,2,2))
```

Goals

- Curves of $P(\text{state} \mid t)$ are as easy as `survfit`
- Multi-state fits are as easy as `coxph`
- Secondary summaries E(time in state), E(visits to state), …
- Standardized data $\longrightarrow$ better data tools
  - Cannot be in two places at once
  - If at risk, must be someplace
  - Gaps and teleports are viewed with suspicion
  - Don't make the user break the rules
  - Immortal time bias is pernicious.
- Robust variance (dfbeta matrix) for all estimates
  - Correct variance with IP weights
  - Variance of derived quantities
- These are the tools that I use.

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- Don't bugger it up

Data check

```
> check <- survcheck(Surv(tstart, tstop, event) ~ 1,
                     data=mydata, id=id)
> check$transitions
         to
from       CR SCT relapse death (censored)
  (s0)    443 106      13    55         29
  CR        0 159     168    17        110
  SCT      11   0      45   149        158
  relapse   0  99       0    99         28
  death     0   0       0     0          0
> #
> check$flag
 overlap      gap     jump teleport
       0        0        0        0
```

Complex multi-state coxph models

```
temp <- list(Surv(tstart, tstop, event) ~ age + trt,
             1:c("SCT", "Fail")  ~ sex / common,
             "SCT":"Fail" ~ hgb)
fit2 <- coxph(temp, data=mdata, id=id, x=TRUE)
```

Yet to do

- Nag level

Yet to do

- Nag level
- Unnamed state
  - “ ”
  - ()
  - (s0)
- Methods: [, coef, plot, print, quantile, anova, vcov, extractAIC, . . .
- More tests
- Check 500 other packages
- Submit to CRAN

Hitchhiker's guide to survival

Causal estimates

- A very important aspect of time-to-event data
- Properties:
    1. Prediction can be verified
        - P(alive at 2 years) = 27%
        - I can watch you for 2 years and find out
    2. Prediction is additive over subjects
        - $p_1 = .27, p_2 = .83, p_3 = \ldots$
        - population prediction $= (1/n) \sum p$
    3. The HR does not satisfy this, P(state) does.
- The HR does not satisfy this, P(state) does.

survival