Multi-state models

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Context

- I am a statistician working in medical research.
- Mayo is a tertiary care center
- Most of the question I work with are "time until . . ."
  - death due to advanced cancer
  - recurrent episodes in Crohn's disease
  - waiting time until organ transplant
  - . . .

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Censoring

Key issue: it is time to do the analysis, and not every subject has yet had an event.
This is most often encoded as a pair of variables using 0/1 for the status where 1= complete observation and 0= censored.

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```
> library(survival)
> test <- data.frame(time=   c(9, 3,1,1,6,6,8),
                     status=c(1,NA,1,0,1,1,0),
                     x=     c(0, 2,1,1,1,0,0))
> test
  time status x
1    9      1 0
2    3     NA 2
3    1      1 1
4    1      0 1
5    6      1 1
6    6      1 0
7    8      0 0
> #
> Surv(test$time, test$status)
[1] 9  3? 1  1+ 6  6  8+
```

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Methods

- "time" as incomplete data
  - (t, δ) and covariates X
  - The traditional viewpoint
  - Won't be seen again.

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Methods

- "time" as incomplete data
  - (t, δ) and covariates X
  - The traditional viewpoint
  - Won't be seen again.
- Multi-state models
  - Subjects go from state to state
  - Some have many transitions
  - Some have zero
  - There is no "incomplete" data.
  - Much easier to think about multiple events

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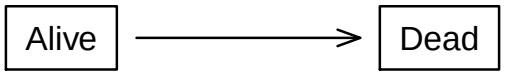
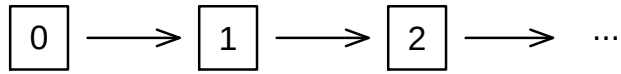
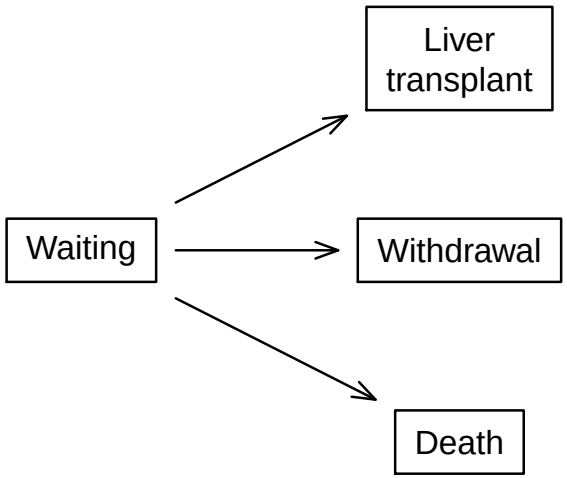
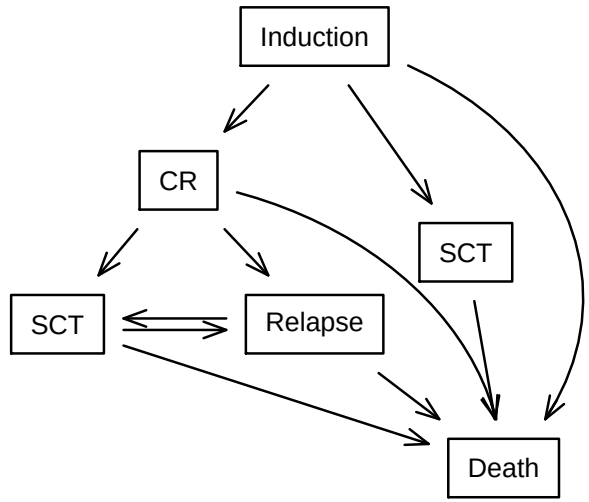

Alive
Dead


0
1
2
...


Liver transplant
Waiting
Withdrawal
Death


Induction
CR
SCT
SCT
Relapse
Death

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Quantities

- 1. Event rates (arrows): λ_{jk}
- 2. Probability in state: $p(t) = (p_1, p_2, \ldots p_k)(t)$
- 3. E(time in state)
- 4. Pr(ever visit a state) or lifetime risk
- 5. Visit times for a state
- Number 1 is not enough

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- 5. Visit times for a state
- Number 1 is not enough
- Statisticians in the field tend to flip back and forth between 1 and 2, which can confuse onlookers.

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Event rates

- Simple rate $r = \sum d_i / \sum t_i$
  $P(T > t) = \exp(-rt)$
- labeled as $r(t)$, $h(t)$, $\lambda(t), \alpha(t)$
- Underpin
  - Kaplan-Meier curves
  - Proportional hazards (Cox) model
  - Log-rank test

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- Underpin
  - Kaplan-Meier curves
  - Proportional hazards (Cox) model
  - Log-rank test
- Martingale theory gives a formal underpinning.
  - $(N(t), Y(t))$ and $X(t)$ or $Z(t)$
  - $N_{ij}(t)$ = number of events so far, subject i, event type j
    $Y_{ij}(t) = 1$ if subject is at risk for event type j at time t

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Graunt's Life Table (1662)

Age Interval	Proportion Deaths in Interval	Proportion Surviving until start of Interval
0–6	0.36	1.00
7–16	0.24	0.64
17–26	0.15	0.40
27–36	0.09	0.25
37-46	0.06	0.16
47-56	0.04	0.10
57-66	0.03	0.06
67-76	0.02	0.03
77-86	0.01	0.01

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Event rates

- Old idea
- The effect of a covariate is often a change in event rate
  - Add 16 year old driver to your insurance
  - Acute disease (Cox model)
- Good theory (martingale)

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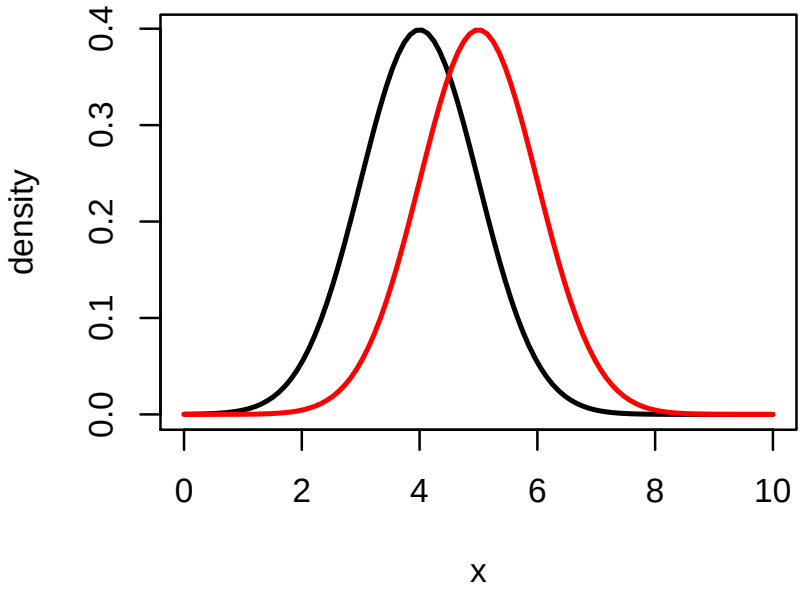
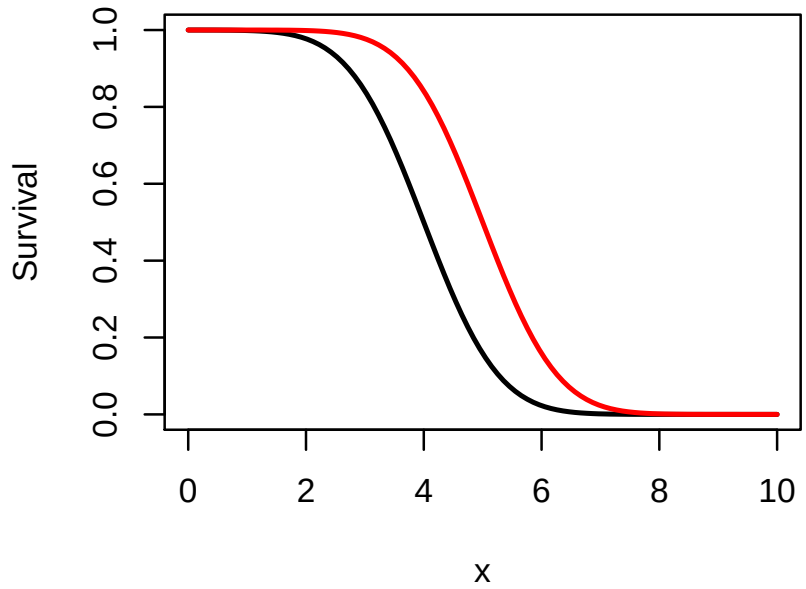
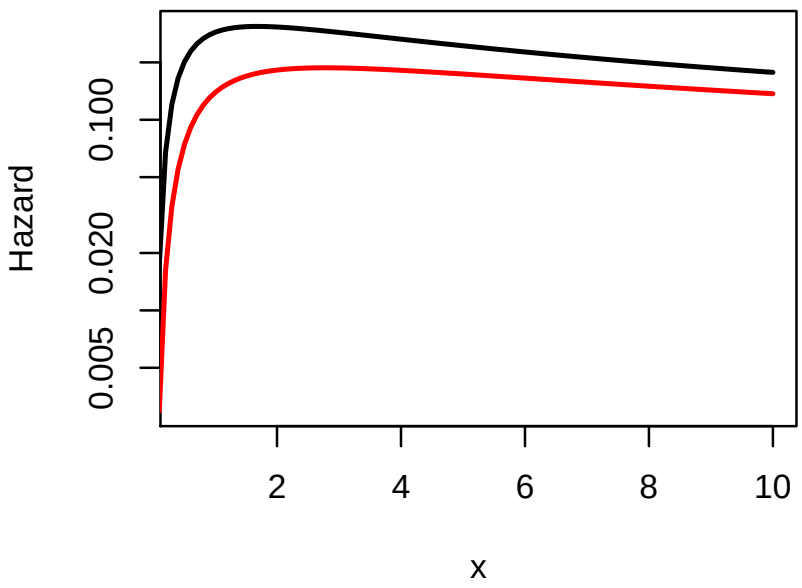
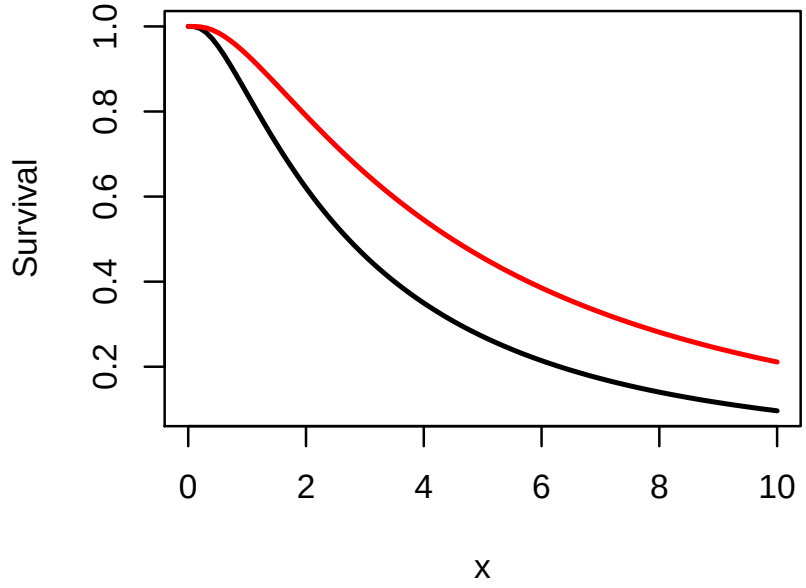
Mayo Clinic Study of Aging









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Key thesis

- For acute disease processes the classic triad of KM, Cox, log-rank works really well.
  - One outcome dominates all others.
  - Through the early 1990s these were the problems I saw.

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Key thesis

- For acute disease processes the classic triad of KM, Cox, log-rank works really well.
  - One outcome dominates all others.
  - Through the early 1990s these were the problems I saw.
  - Not anymore
- Multiple outcomes are the rule, not the exception.
- It's time to move on.
- And it isn't that hard.

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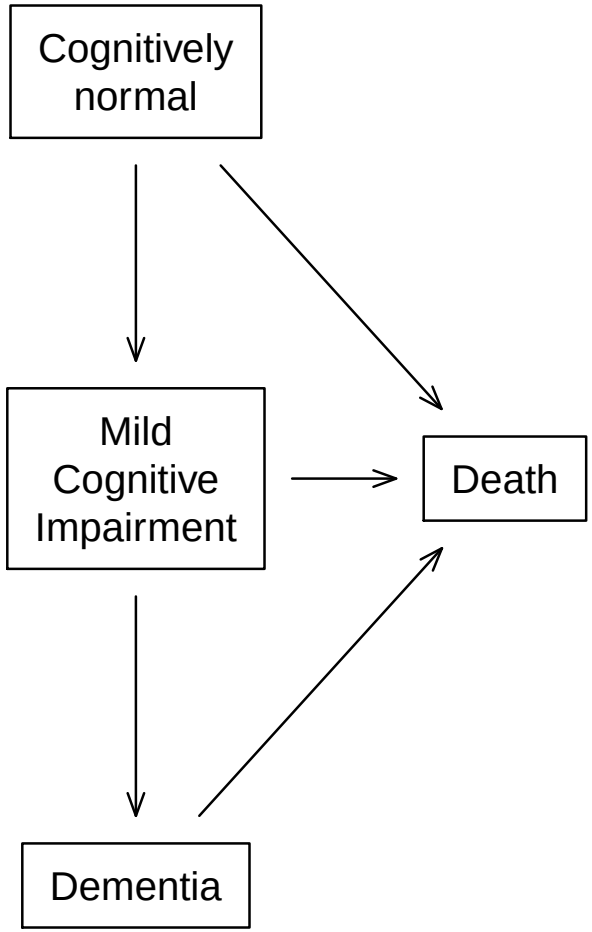
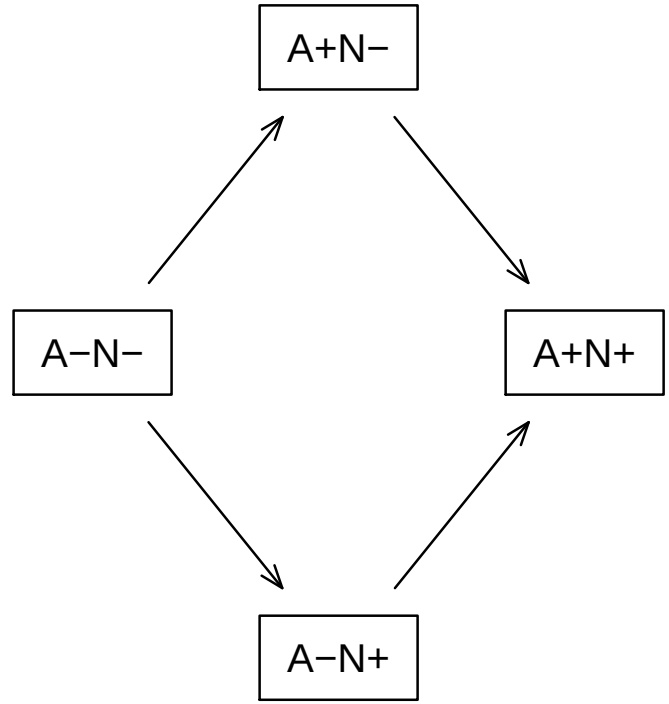

Cognitively normal
Mild Cognitive Impairment
Death
Dementia


A+N−
A−N−
A+N+
A−N+

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Informative censoring

- All time to event models assume *uninformative censoring*.
- You cannot cease following someone because of something that will happen in the future.
  - Look ahead: analysis of those who "comply with the treatment"
  - People who drop out because they are about to fail MDPIT trial (Oakes, JASA 1993; 88:44-49)
  - Only those who are sick respond to queries.

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  - People who drop out because they are about to fail MDPIT trial (Oakes, JASA 1993; 88:44-49)
  - Only those who are sick respond to queries.
  - The fact that someone dropped out allows you to better guess their death rate.

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2. Probability in State

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Transplant outcome

The data set that first forced me to explore multi-state methods.

- All patients added to the liver transplant waiting list during 1990-1999 at Mayo Clinic
- Corresponds to an explosion in LT programs and patients
- The median waiting time at the start is 45 days, 446 days at the end
- Question: did death on the waiting list increase?

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Note

The current liver transplant waiting list, handled by the United Network for Organ Sharing (UNOS), is managed in a much more sophisticated way than it was at the time of this data. Do not make conclusions about current conditions from this analysis.

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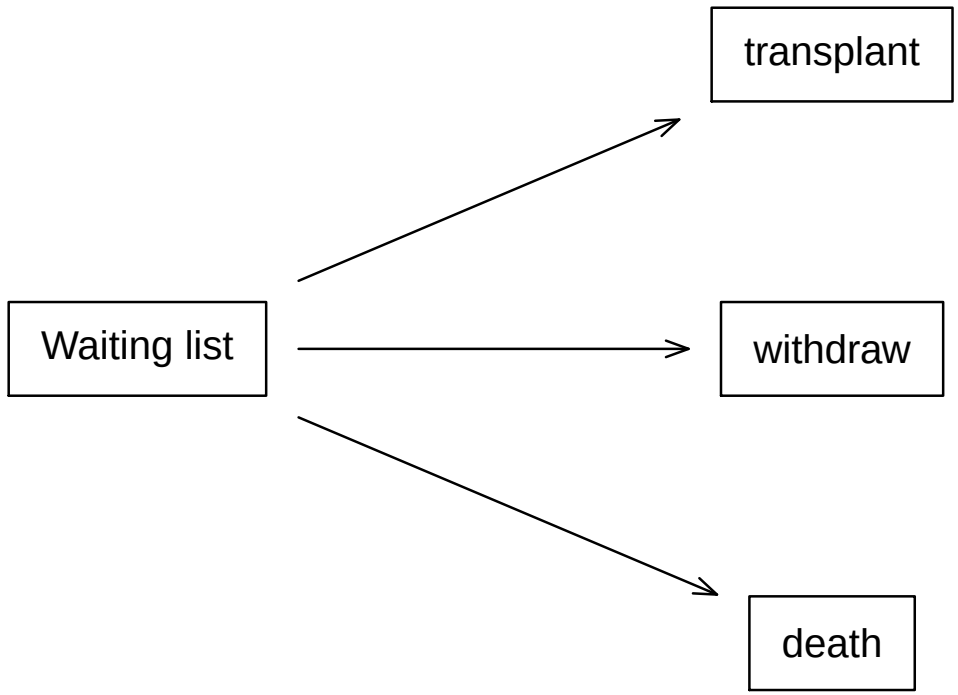
Competing risk



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Impact of Waiting Time

- All Mayo patients listed from Feb 1990 to Aug 1999
- 815 subjects: 636 OLT, 66 death, 37 withdraw, 76 censored

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Impact of Waiting Time

- All Mayo patients listed from Feb 1990 to Aug 1999
- 815 subjects: 636 OLT, 66 death, 37 withdraw, 76 censored
- Primary question: Did increased waiting time harm survival? For whom?
- `transplant` data set is included in R
  - age, sex, blood type, year of listing
  - follow-up time and event = (death, ltx, withdraw, censor)

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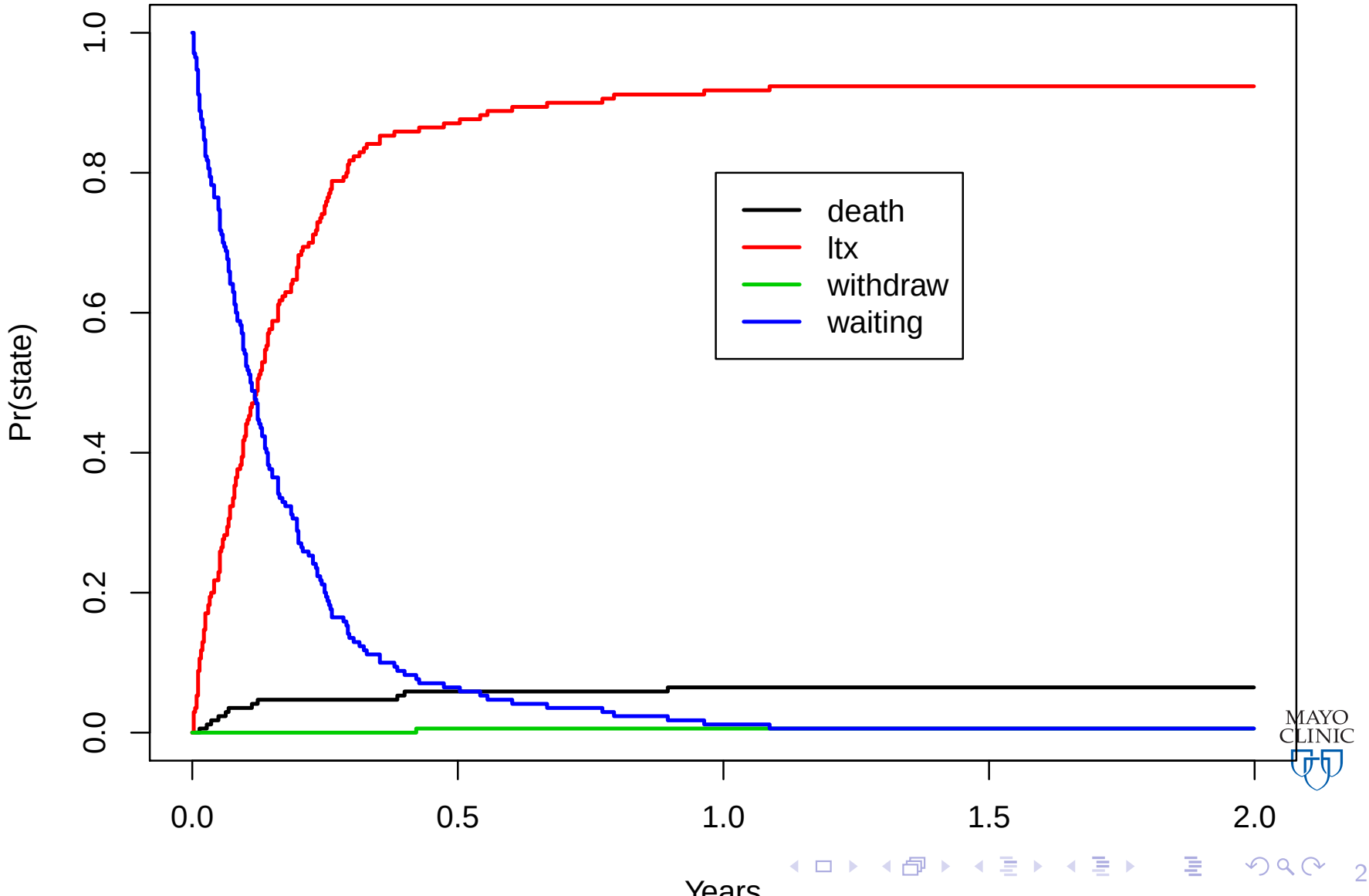
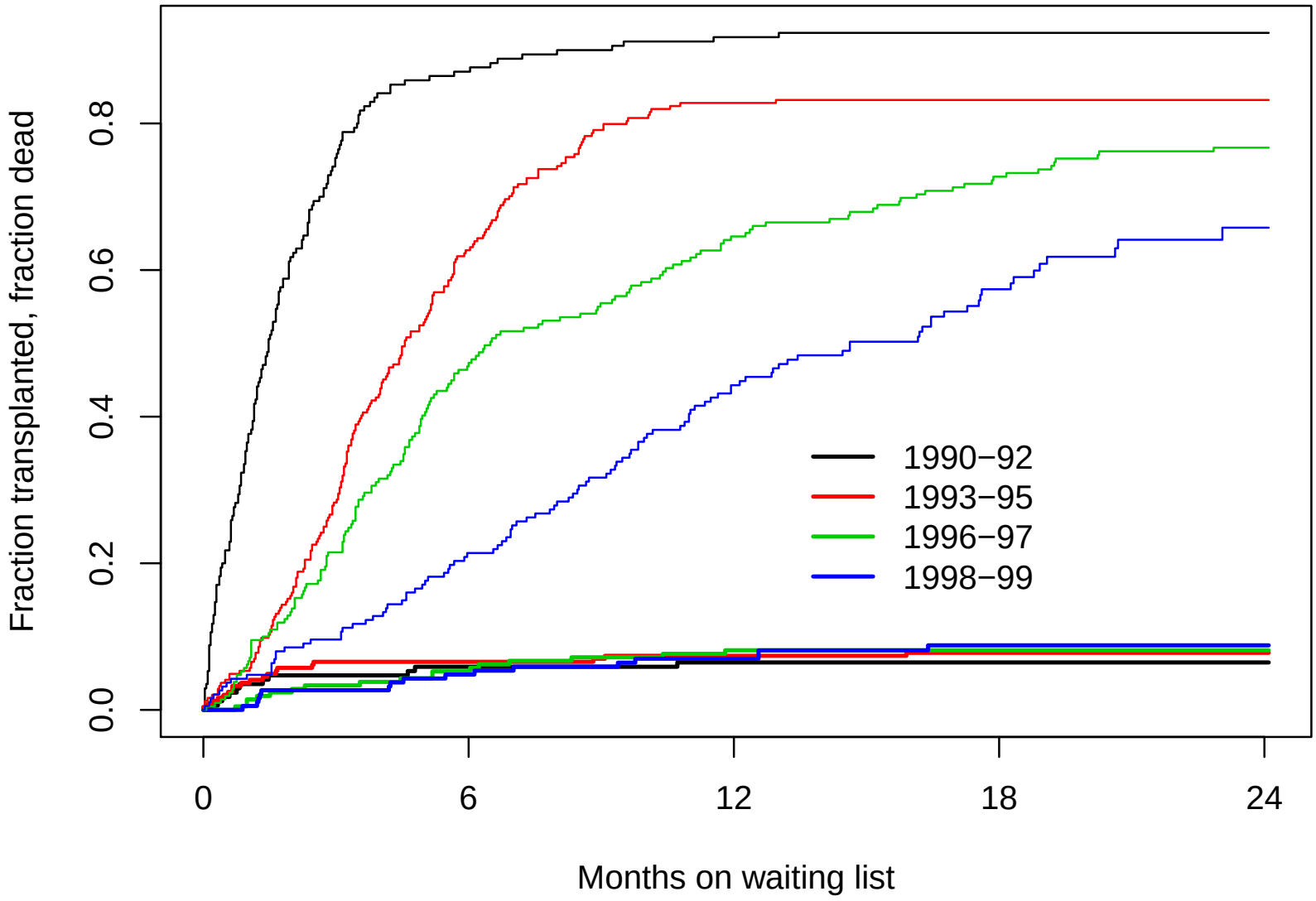
Aalen-Johansen estimate

```
> afit <- survfit(Surv(futime, event)~ 1, data=transplant)
> plot(afit, col=1:4)
```




Fraction transplanted, fraction dead
0.0
0.2
0.4
0.6
0.8
0
6
12
18
24
Months on waiting list
1990−92
1993−95
1996−97
1998−99

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plots

- There are 16 curves = 4 states * 4 periods
- In R the curves can be treated like a matrix
  - `pfit[1,]` = all states, first period
  - `pfit[,1]` = death state, all periods
- Useful, since a primary display challenge is artistic: how to not be overwhelmed with a spaghetti plot.

```
> pfit <- survfit(Surv(futime, event) ~ period, transplant)
> plot(pfit[,1:2], ...)
```

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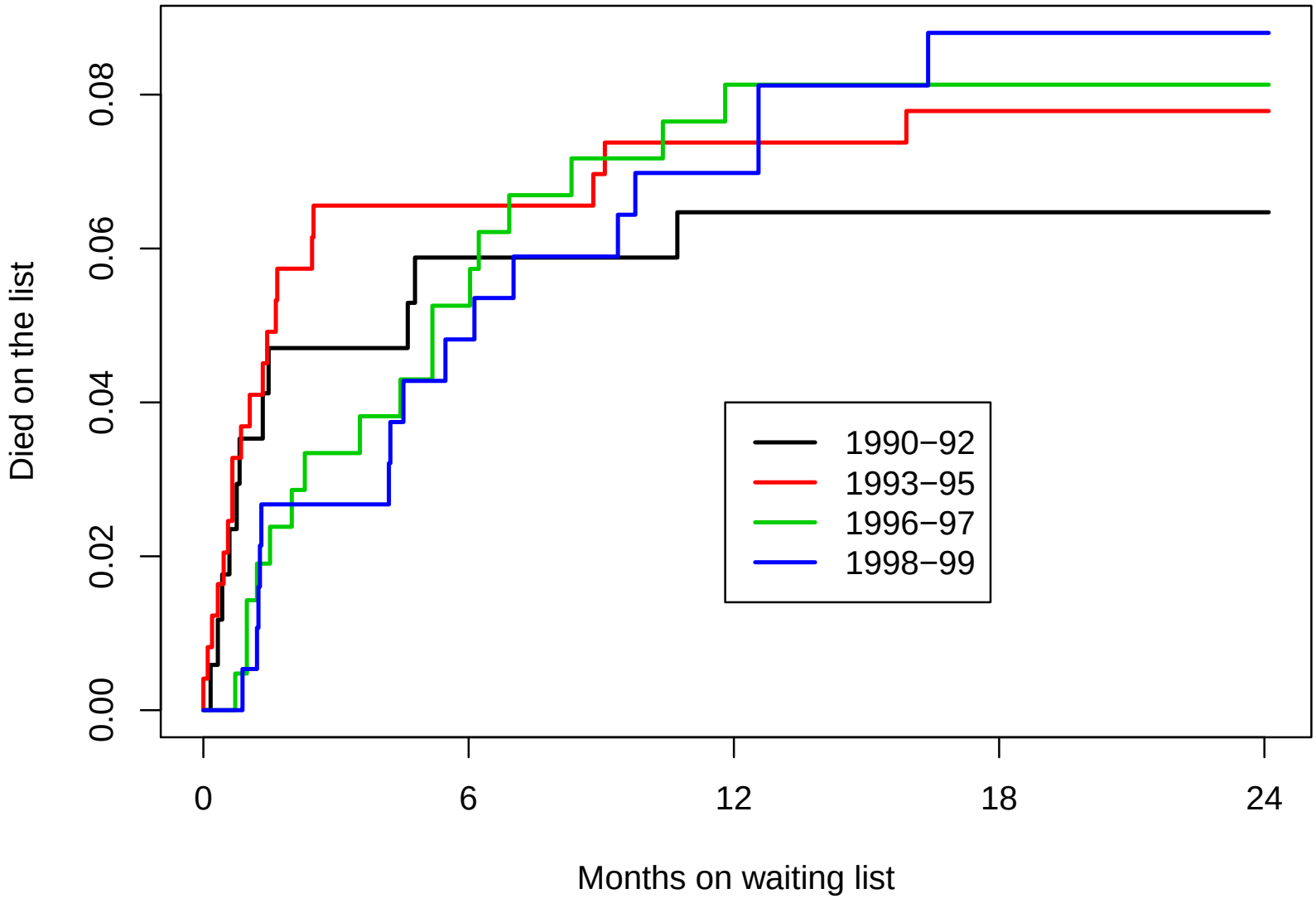
Died on the list
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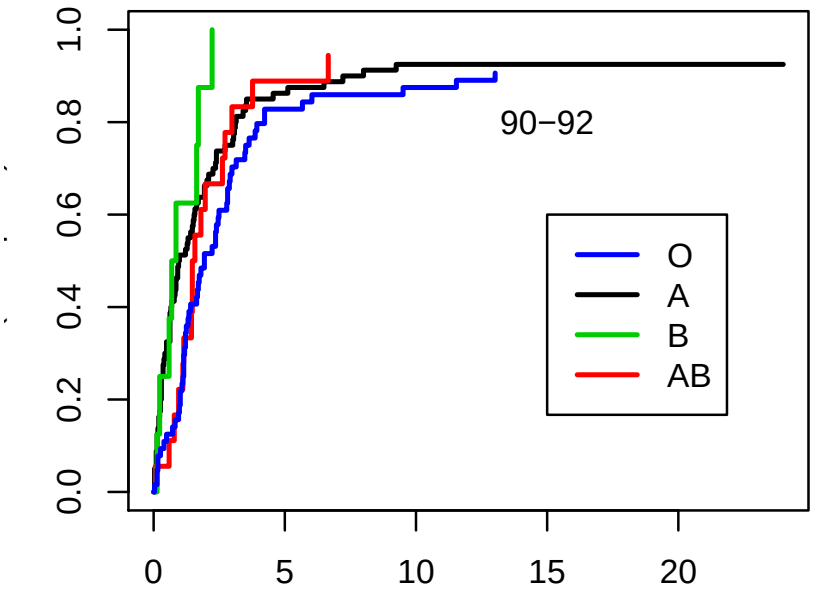
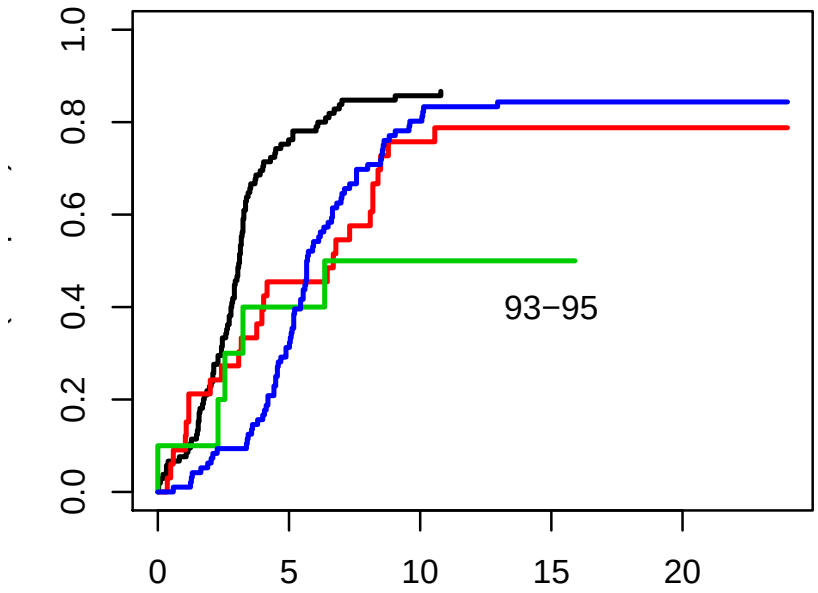
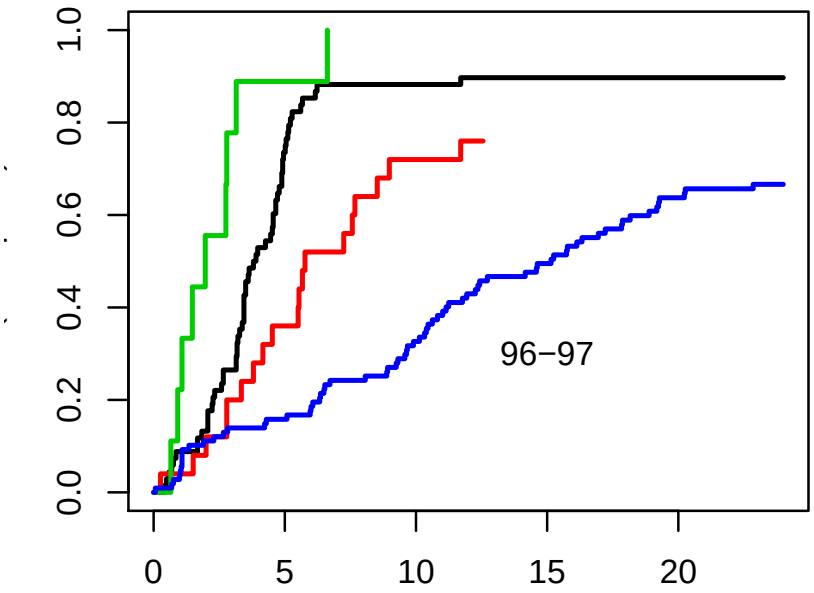
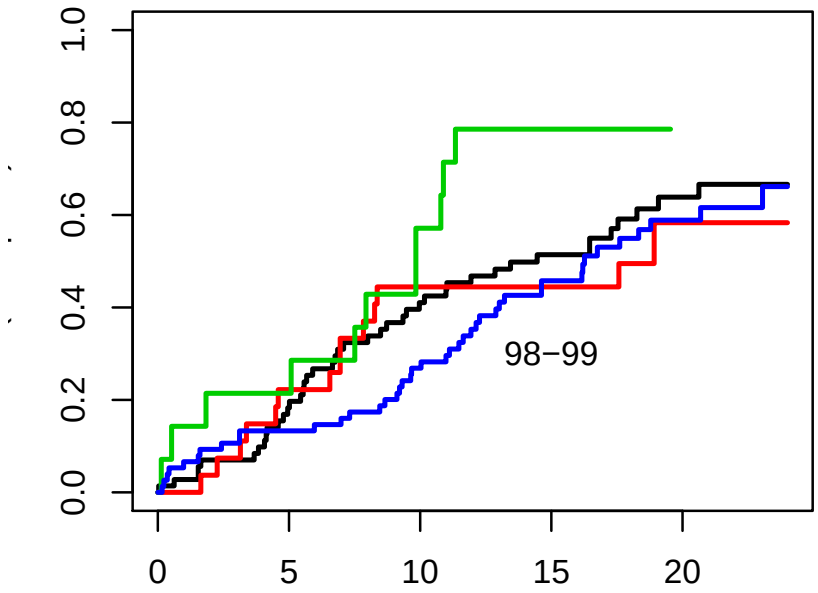

90−92
O
A
B
AB
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20


93−95
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20


96−97
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20


98−99
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20

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Wrong approach

Fit a survival model of time to death, treating transplant and withdrawal as censored.

```
> badfit <- survfit(Surv(futime, event=="death") ~ period,
                    data= transplant)
> plot(badfit, fun='event', col=1:4, mark.time=F, lwd=2,
      xscale=365.25, xlab="Years since entry", ylab="Death")
> legend(.5, .9, levels(period), lty=1, lwd=2, col=1:4, bty='n')
```

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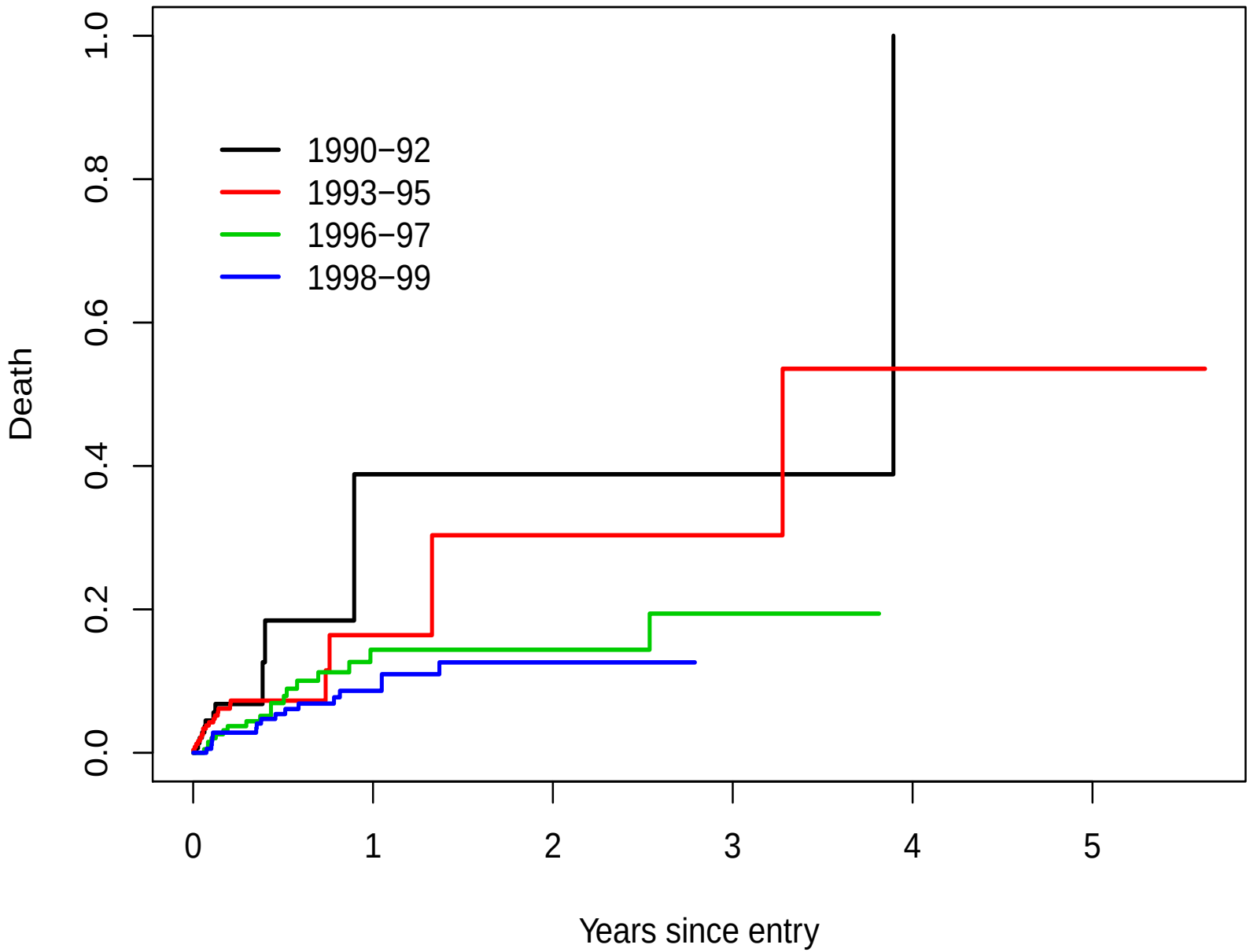
1990−92
1993−95
1996−97
1998−99
Death
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Years since entry

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What's wrong?

- Major issues
  1. An estimate of death rates for a population *where transplant and withdrawal were abolished*. That was not the question.
  2. The estimate assumes uninformative censoring, i.e., those who were removed due to transplant were a random sample of those at risk for death. Rarely true, if ever.
- Unreliable estimate of an uninteresting quantity.

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- Unreliable estimate of an uninteresting quantity.
- The multi-state curve estimates the fraction of subjects who will *actually experience* death before transplant.
  - Aalen-Johansen estimate replaces the Kaplan-Meier
  - an observable quantity

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This class has 3 main points

- multi-state models are an important addition to your modeling toolbox
- they can yield important insights into your data
- they are easy to implement with current software

Sub-theme: interpretation can be complicated – you will be required to THINK.

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If you make someone think that they are thinking, They will love you for it. If you make them actually think, They will hate you for it. This explains why people love pie charts and hate more effective graphs. Greg Snow R-help (December 2009)

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Focus on examples

- When
- How
- Usefulness

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Resources

- H. Putter, M Fiocco and R. B. Geskus, Tutorial in biostatistics: Competing risks and multi-state models. Stat in Medicine, 2007:2389-2430.
- T. Therneau, Competing Risks, R survival package.
- T. Therneau, Multi-state models, R survival package.
- J. Beyersmann, A Allignol, M. Schumacher, Competing and multistate models in R.
- R. Cook and J. Lawless, Multi-state models for the analysis of life history data. 2018

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Math: the KM estimator

Let t_1, t_2, ... be the unique death times.

$$\lambda(t_i) = d_i/n_i \qquad \text{fraction of deaths at } t_i$$

$$KM(t) = \prod_{s \le t} [1 - \lambda(s)]$$

$$FH(t) = \prod_{s \le t} \exp[-\lambda(s)]$$

Cox model code can use a Kaplan-Meier analog (Kalbfleish-Prentice) or a Fleming-Harrington analog (Breslow); the latter is easier to compute.

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Multi-state: Aalen-Johansen estimator

At each time create a transition matrix

$$H = \begin{pmatrix} \lambda_{11}(t) & \lambda_{12}(t) & \lambda_{13}(t) & \lambda_{14}(t) \\ \lambda_{21}(t) & \lambda_{22}(t) & \lambda_{23}(t) & \lambda_{24}(t) \\ \lambda_{31}(t) & \lambda_{32}(t) & \lambda_{33}(t) & \lambda_{34}(t) \\ \lambda_{41}(t) & \lambda_{42}(t) & \lambda_{43}(t) & \lambda_{44}(t) \end{pmatrix}$$

- $\lambda_{ij}(t) = d_{ij}(t)/n_i(t)$
  $=$ number who went from $i \to j$ / number in state i
- Each row sums to 1
- Diagonal $=$ those who didn't go anywhere

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Then

$$p(t) = p(0) \prod_{s \le t} H(s)$$
$$\approx p(0) \prod_{s \le t} \exp(H(s) - \mathcal{I})$$

- the i, j element of $P(t)$ is the probability that someone who started in state i at time 0 will be in state j at time t.
- $p(0)$ = starting distribution, usually $(1, 0, 0, \ldots)$
- $p_j(t) = \Pr(\text{in state } j \text{ at time } t)$, $\sum_j p_j(t) = 1$
- $p(t)$ is the Aalen-Johansen estimator
- Many (most) theory books use $dA(t)$ (rows sum to 0) and $I + dA(t)$ (rows sum to 1).

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Alternate view

- Treat survival as a Poisson process.
  1. Divide time into a bunch of intervals
  2. Within each interval calculate the naive rate of transition $r(t)$ for death
     = (number making the transtion) / time at risk
  3. Markov model estimate is $p(0)[r_1 t_1][r_2 t_2] \ldots$.
- For a 2 state alive-dead model this yields the "actuarial" estimator.
  - Once quite common.
  - Applies directly to tabulated data (like Graunt's).
  - Nuisance: how wide should the intervals be?

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- The theory still works out! Kaplan and Meier (1958)
- Pet peeve: "Actuarial survival was calculated using the method of Kapan and Meier".

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- The theory still works out! Kaplan and Meier (1958)
- Pet peeve: "Actuarial survival was calculated using the method of Kapan and Meier".
- For the general multi-state model, let the widths of the intervals go to zero. The theory still works out! Aalen and Johansen (1978)

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Exercises

1. For the two state alive $\rightarrow$ dead model, show that $p_1(t)$ from the Aalen-Johansen estimate = Kaplan-Meier.
2. For the competing risks model show that $p(t)$ = "cumulative incidence" estimator.
3. Explain why it took 25 years for statisticians to adopt the KM.
4. Explain why it has been over 35 years for the AJ, and it still is rare. (We are getting even slower?)

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In the R survival package

```
fit <- survfit(Surv(time, status) ~ group, data=mydata)
```

- If `status` is a 0/1 or true/false variable, this gives the Kaplan-Meier + Greenwood estimate of variance
- If `status` is a categorical variable (factor), this gives the Aalen-Johansen estimate + infinitesimal jackknife estimate of variance.
- Same commands to create, print, plot, or extract values from the curves.

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IJ estimator

Assume a case weight vector of w, and for each subject k compute

$$U_{jk}(t) = \left.\frac{p_j(t)}{w_k}\right|_w$$
$$V(t) = U'(t)U(t)$$

- The robust variance for a Cox model is an IJ estimate
- So is the Horvitz-Thompson variance estimate (survey sampling)
- The working independence variance of GEE models

...

- For a 2 state alive-dead model, the IJ estimate = Greenwood's estimate
  - empirically verified for a large number of data sets
  - Proof: Anne Eaton

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AJ curves, 2 state model

- $p(t)$ = (fraction still alive, fraction who have died)(t)
- Some disciplines prefer to plot prob(alive),
  - the classic survival curve that starts at 1 and goes down
  - some *insist* on it
- Some disciplines prefer to plot prob(event), which starts at 0 and goes up
- Convention and history, not science.
- Pocock and Altman, Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002.

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AJ curves, multi-state

- In a multi-state model $p(t)$ sums to 1 so one of the curves can be omitted from a plot
- Most people omit Pr(still in the entry state) as it is the least interesting
- As a result all the curves go up

MAYO CLINIC

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- In a multi-state model $p(t)$ sums to 1 so one of the curves can be omitted from a plot
- Most people omit Pr(still in the entry state) as it is the least interesting
- As a result all the curves go up
- Some users/disciplines/journals are so bothered 'uphill!' that they suggest a plot of $(1 - p_1(t))$, $(1 - p_2(t))$, etc.
- Imagine a plot of customers in at DFO = (fraction not in the shoe dept, fraction not in the food court, fraction not in toys, ...)

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Example: Lymphoma treatment trial

The canonical treatment path for some hematologic malignancies is
entry $\longrightarrow$initial trt $\longrightarrow$CR $\longrightarrow$BMT $\longrightarrow$relapse
Not everyone follows this ideal path

- The initial or conditioning treatment is designed to remove the large majority of malignant cells
- CR: complete response = no overt evidence of malignancy
- BMT/SCT: bone marrow transplant or stem cell transplant = high intensity chemotherapy that will ablate the marrow and requires rescue with hematologic stem cells
- relapse: reappearance of disease after CR

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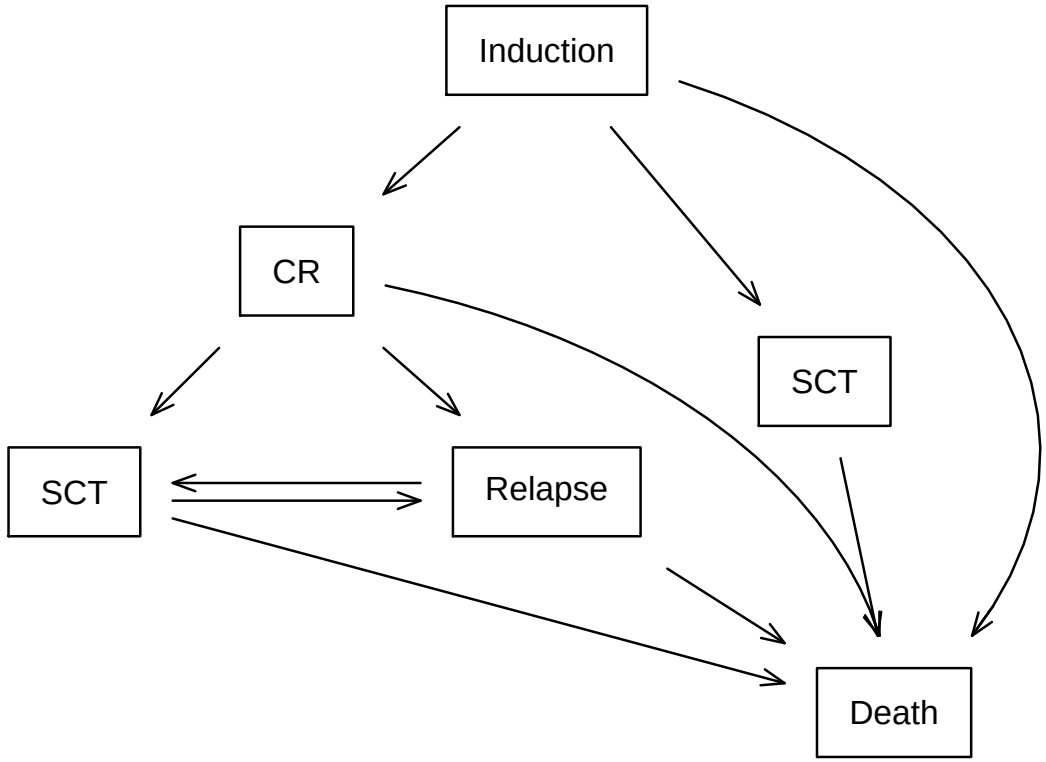

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- Subjects can (and do) traverse every arrow in the diagram
- The vignette on multi-state models in the survival package explores this data set.
- `cran.r-project.org/web/packages/survival/vignettes/multi.pdf`

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```
> myeloid[1:5,]
  id trt futime death txtime crtime rltime
1  1   B    235     1     NA     44    113
2  2   A    286     1    200     NA     NA
3  3   A   1983     0     NA     38     NA
4  4   B   2137     0    245     25     NA
5  5   B    326     1    112     56    200
```

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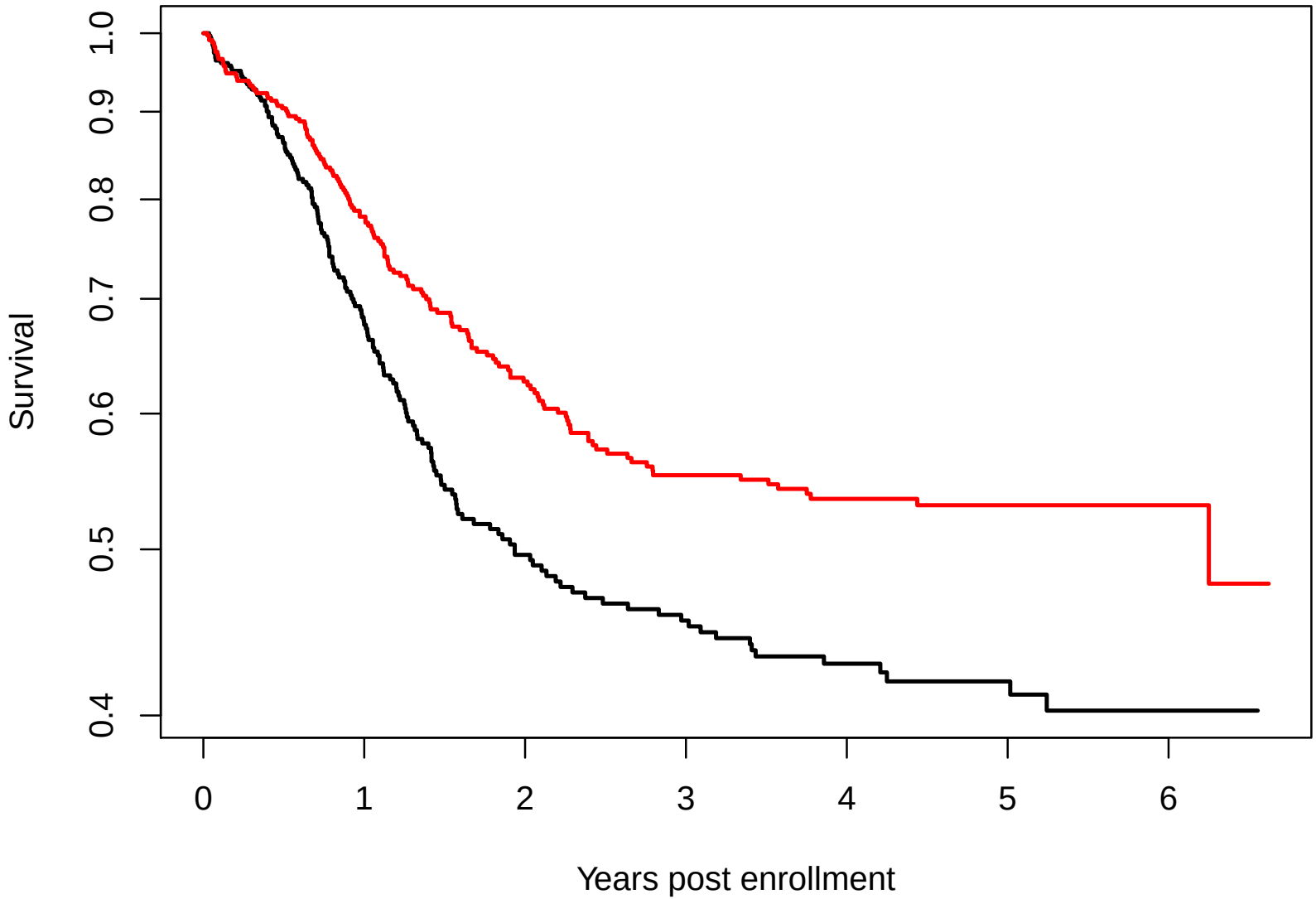
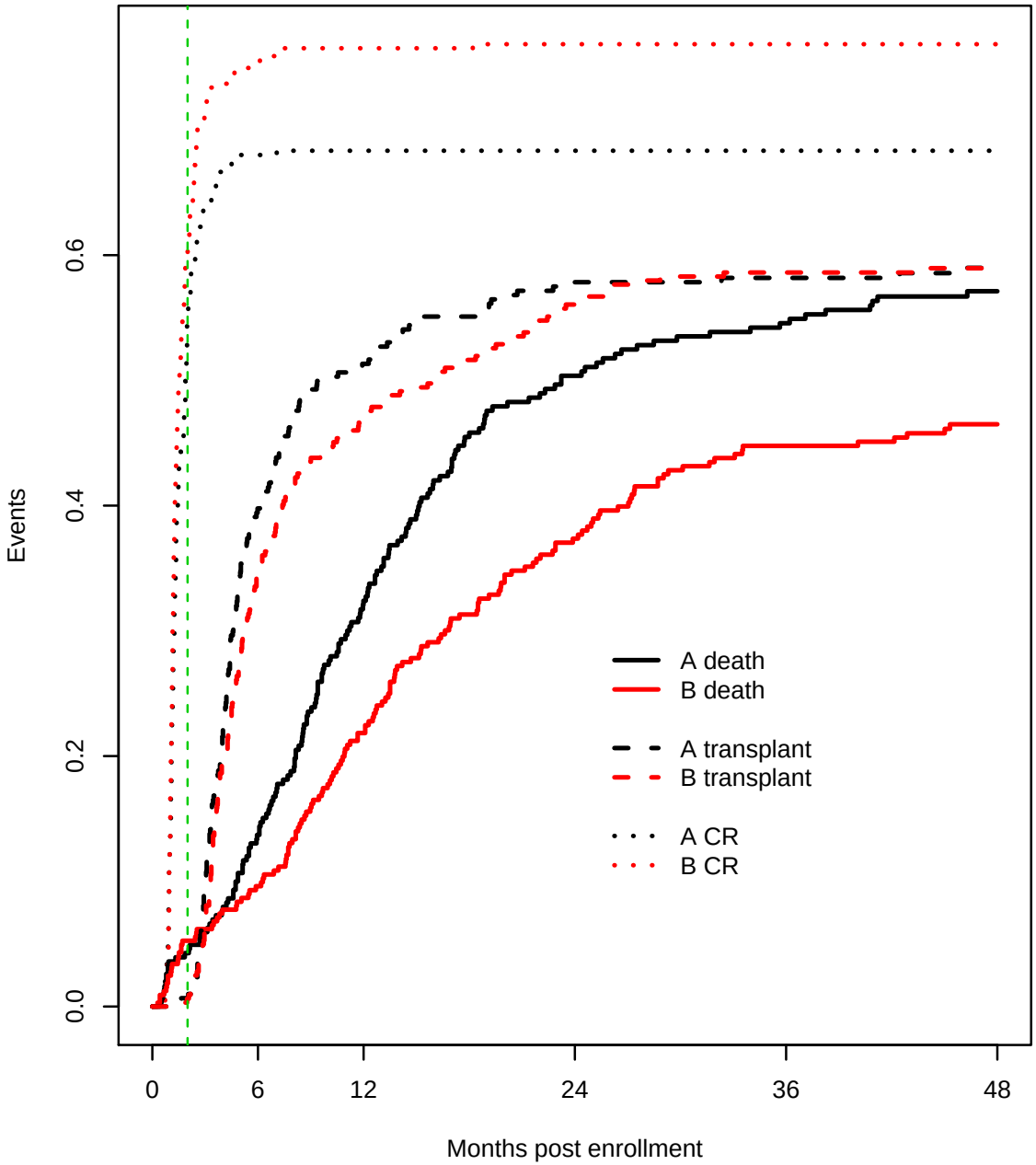
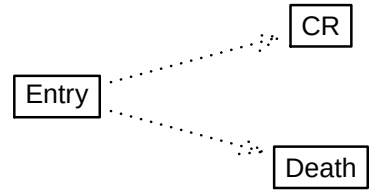
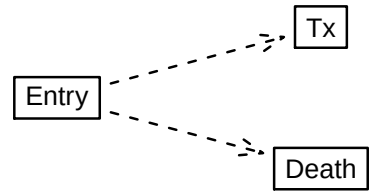
Overall survival

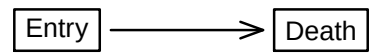


MAYO CLINIC


Events
0.0
0.2
0.4
0.6
0
6
12
24
36
48
Months post enrollment
A death
B death
A transplant
B transplant
A CR
B CR


Entry
CR
Death


Entry
Tx
Death


Entry
Death

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- Almost all of the CR occur by 2 months (green line)
- The additional responses for arm B happen after this

MAYO CLINIC

- Almost all of the CR occur by 2 months (green line)
- The additional responses for arm B happen after this
- Transplants start at 2 months, more A than B!
- Survival advantage for B at 5 months

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Computation

- For each different state space configuration, create a data set.
  - id, (time1, time2], endpoint, covariates
  - The interval from time1 to time2 is terminated with a given endpoint at time2.
    - censor, dead
    - censor, CR, death before CR
    - censor, SCT, death before SCT
- A familiar task for time-dependent covariates.
- Fit AJ curves for each, create a mashup plot.

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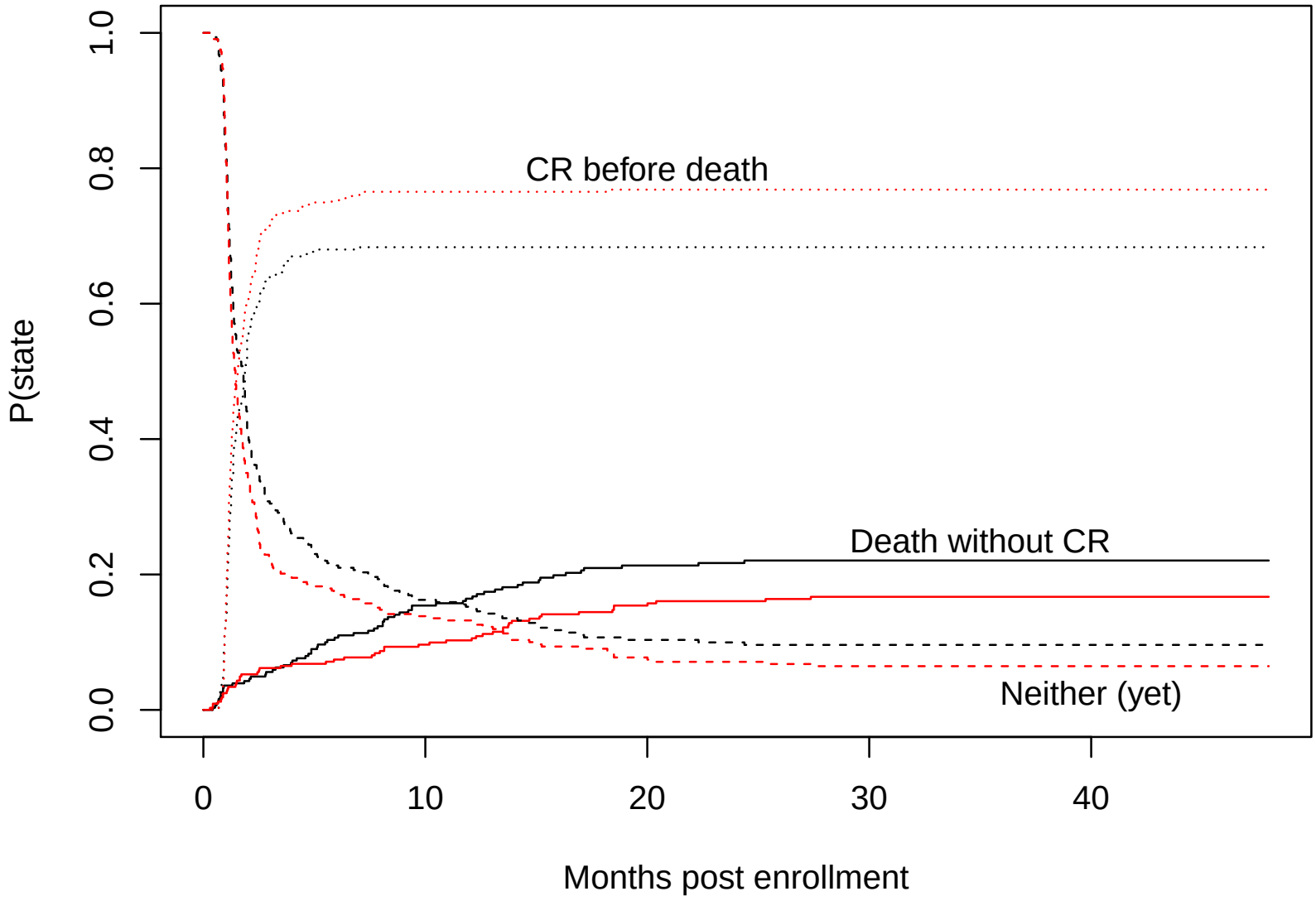
P(state
0.0
0.2
0.4
0.6
0.8
1.0
CR before death
Death without CR
Neither (yet)
0
10
20
30
40
Months post enrollment

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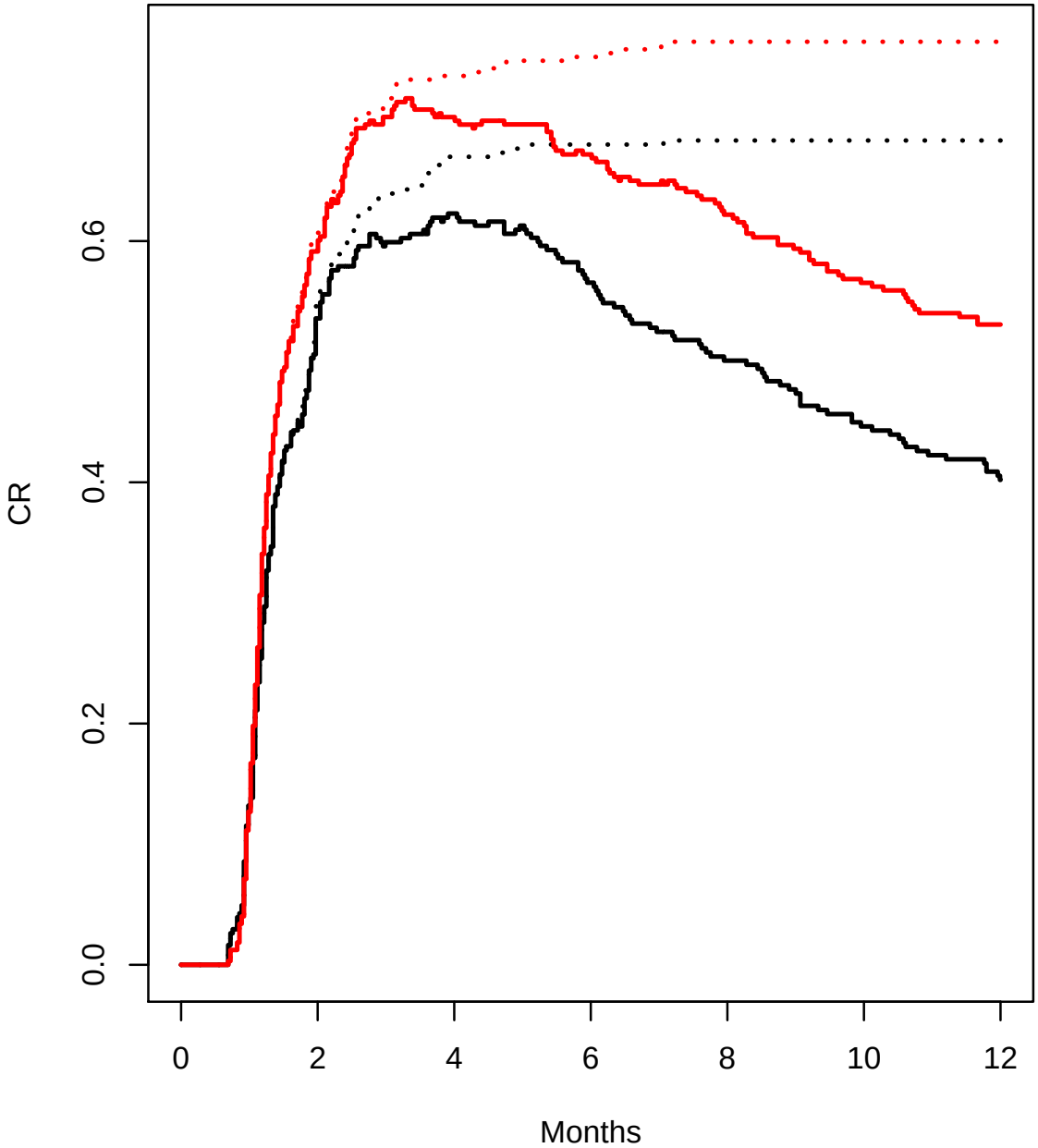
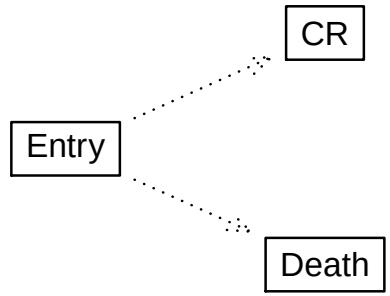
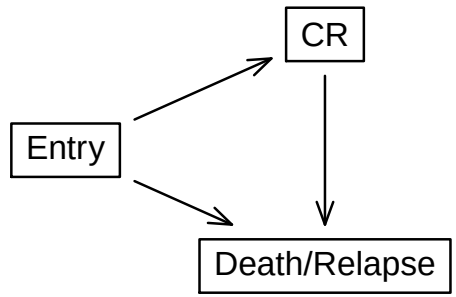

CR
0.0
0.2
0.4
0.6
0
2
4
6
8
10
12
Months


CR
Entry
Death


CR
Entry
Death/Relapse

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Treatment arm B has more CRs and they are more durable.

- "But I want numbers"
- Values and se at particularly follow-up times.
  - A at 6, 12, 18 months: .56(.03), .40(.03), .31(.03)
  - B at 6, 12, 18 months: .67(.03), .53(.03), .45(.03)
- Mean time in state (sojourn time)
  - *restricted* mean, up to a given time point (24)
  - A: 9.6 (0.5), B: 12.3 (0.5)
- "But I want p-values"
  - B-A = 2.7 (.77), $p < .001$

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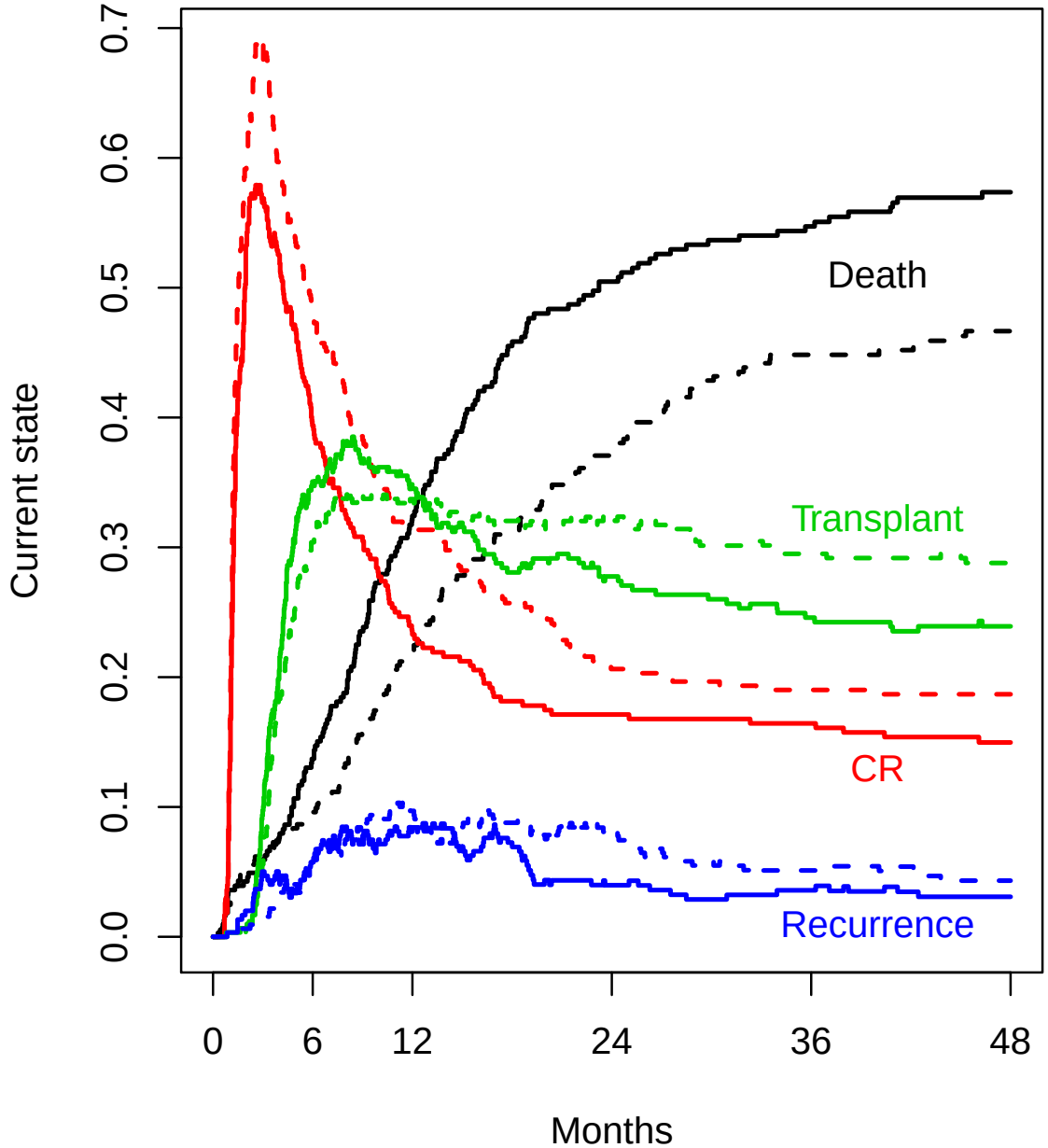
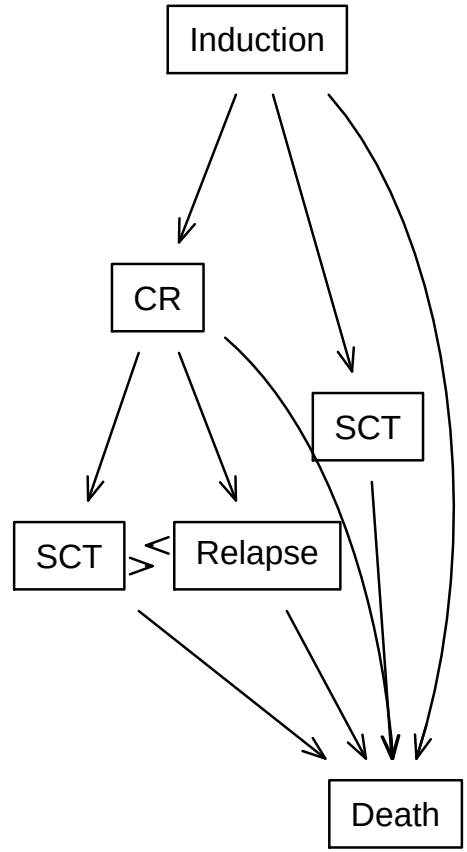

Current state
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Death
Transplant
CR
Recurrence
0
6
12
24
36
48
Months


Induction
CR
SCT
SCT
Relapse
Death

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Data

- Creating the prior curves is about
  - 70% create the data
  - 10% compute the fit
  - 20% draw the picture

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Final figure

```
sfit4 <- survfit(Surv(tstart, tstop, event) ~ trt,
                 data= data2, id=id)
```

	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	transplant
5	2	A	200	286	death
6	3	A	0	38	CR
7	3	A	38	1983	censor
8	4	B	0	25	CR
9	4	B	25	245	transplant
10	4	B	245	2137	censor

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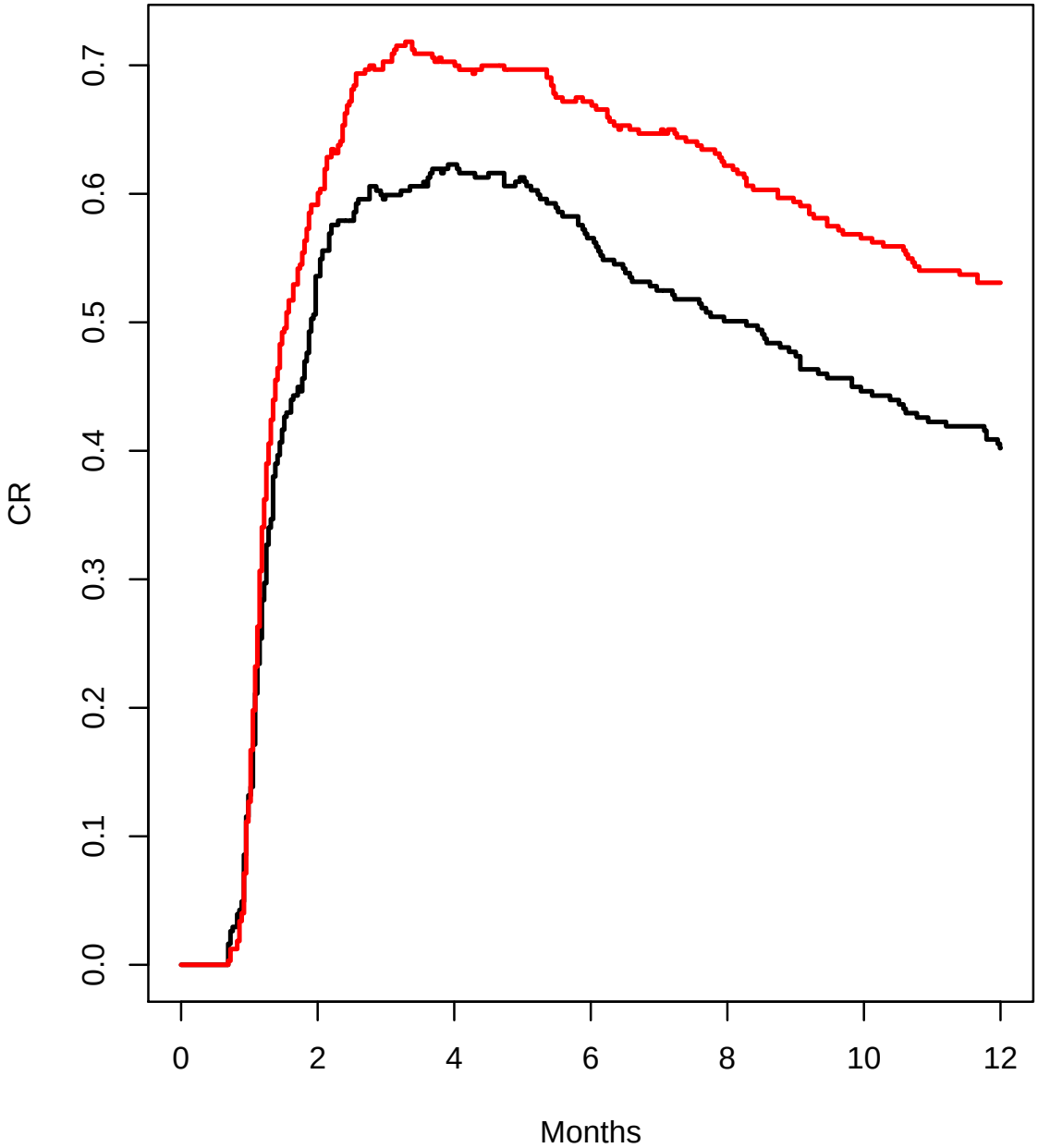
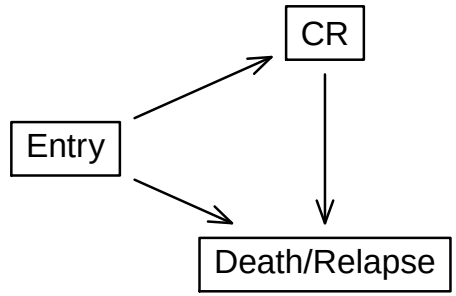

CR
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
2
4
6
8
10
12
Months


CR
Entry
Death/Relapse

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	id	trt	tstart	tstop	event	crstat
1	1	B	0	44	CR	CR
2	1	B	44	113	relapse	relapse
3	1	B	113	235	death	death
4	2	A	0	200	transplant	censor
5	2	A	200	286	death	death
6	3	A	0	38	CR	CR
7	3	A	38	1983	censor	censor
8	4	B	0	25	CR	CR
9	4	B	25	245	transplant	censor
10	4	B	245	2137	censor	censor

- A time period can be broken up
- (0, 5, CR), (5, 20, death)
- (0, 5, CR), (5, 8, censor), (8,15, censor), (15, 20, death)

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```
> sfit4 <- survfit(Surv(tstart, tstop, event) ~ trt, data2, id=id)
>
> sfit4$transitions
            to
from         death  CR transplant relapse
  death          0   0          0       0
  CR            17   0        159     168
  transplant   149  11          0      45
  relapse       99   0         99       0
                55 443        106      13
```

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Building data sets

- Think through the special cases
  - CR and transplant on the same day
  - MGUS data: progression and death
  - PAD data set: a joint left/right amputation
  - R survival does not allow a zero length time interval
- Build the data set
- Print out and READ some portion of it
- Fit the model

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Warnings

Whenever the data/fit can have multiple transitions for one person

- Remember the `id` statement
- The program has no way of knowing which rows go together without it, and instead will assume subjects have delayed entry
- A wrong answer to the wrong question. (Variance too).

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- Individuals cannot have a "hole" in their follow-up time.
- Example: gaps in follow-up
- Individuals may "skip" states
- Example: panel data
  - Smith enters state 1 at one year
  - The next time we see him, one year later, he is in state 3 but we don't know when he made the transition.
  - msm package

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Sequential Events

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- One of the first applications, widely used.
- Data sets in the survival package (book by Therneau and Grambsch)
  - Sequential events
    - Recurrent bladder cancer
    - Repeated infections in children with chronic granulomatis disease
    - rhDNase for the treatment of cystic fibrosis
    - Failure of kidney catheters
  - Parallel events
    - Left and right eyes in diabetic retinopathy
    - Multiple liver sequelae in a UDCA trial

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Parallel events

- Uncommon
- Decisions
  - Multiple strata?
    - Diabetes: no
    - UDCA in PBC: yes
  - strata by covariate interactions
- Data setup: stacked
- Analysis: robust variance

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Diabetic retinopathy

- Two eyes per subject, one randomized to laser coagulation

```
Call:
coxph(formula = Surv(time, status) ~ trt + juvenile + clust
    data = diabetic)

             coef exp(coef) se(coef) robust se      z
trt      -0.77893   0.45890  0.16893   0.14851 -5.245
juvenile -0.05388   0.94754  0.16211   0.17864 -0.302
                p
trt      1.56e-07
juvenile    0.763

Likelihood ratio test=22.48  on 2 df, p=1.312e-05
n= 394, number of events= 155
```

Sequential events

- Single stratum or multiple strata?
  - Does the baseline risk reset to a new level after each event?
  - CGD data set: no
  - Repeat cardiac events: maybe
- strata by covariate iteractions?
- time scale: age, time since enrollment, time since last event, ...

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Models

- Andersen-Gill model
  - single stratum
  - an event is an event is an event
- Prentice-Williams-Petersen
  - new stratum for each event
  - time normally resets to zero
  - dangerous!
- Wei, Lin, and Weissfeld
  - pretend that we have parallel event data
  - never do this

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cgd

```
    id   treat age    sex tstart tstop status
1    1  rIFN-g  12 female      0   219      1
2    1  rIFN-g  12 female    219   373      1
3    1  rIFN-g  12 female    373   414      0
4    2 placebo  15   male      0     8      1
5    2 placebo  15   male      8    26      1
6    2 placebo  15   male     26   152      1
7    2 placebo  15   male    152   241      1
8    2 placebo  15   male    241   249      1
9    2 placebo  15   male    249   322      1
10   2 placebo  15   male    322   350      1
11   2 placebo  15   male    350   439      0
12   3  rIFN-g  19   male      0   382      0
13   4  rIFN-g  12   male      0   388      0
Call:
coxph(formula = Surv(tstart, tstop, status) ~ treat + age +
    cluster(id), data = cgd)
```

Hidden covariates

- Assume an important covariate Z is not in the model
- Single event model
  - β biased towards zero
  - amount is proportional to $se(\gamma Z)$
- Multiple event model
  - stratify by number of prior events, or
  - add number prior events as a covariate
  - β is severely biased, and can actually change sign
- A random effect per subject can help

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AG simplicity

- For many studies, the coefficient(s) from an AG model often have the same interpretation as an ordinary Cox model
- higher rate $\leftrightarrow$ shorter time to next event
- Cumulative hazard = E(number of events so far)
- Survival curve = Pr(no events at all) is more complex, but often not of interest

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3. Competing risks

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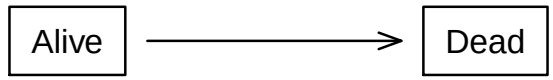

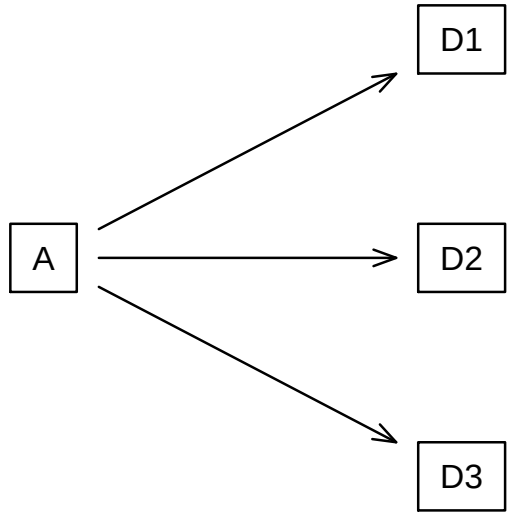

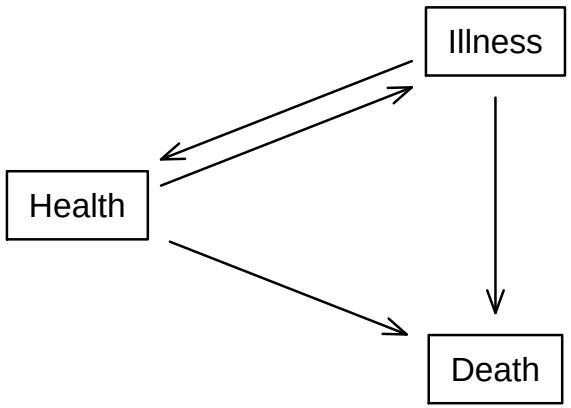

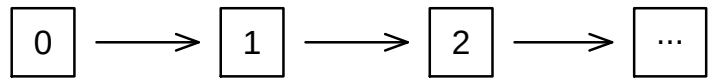

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Monoclonal Gammopathy of Undetermined Significance (MGUS)

- Subjects with a dominant clone in their plasma cell population, but without malignancy ($\geq 2\%$ of plasma cells in the clone).
- Normally found incidentally to other tests.
- Should the patient be worried?
- About 1% per year convert to overt malignancy.
- Essentially independent of age and sex.

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Progression of MGUS

- 1384 subjects with monoclonal gammopathy of undetermined significance (MGUS)
- R. Kyle, New Engl J Med 346:564-569 (2002)
- Questions
  - Pattern of death and progression
  - Relationship to age, sex, hemoglobin, creatinine, and amount of protein in the "spike"

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```
> mgus2[1:5,]
  id age sex  hgb creat mspike ptime pstat futime death
1  1  88   F 13.1   1.3    0.5    30     0     30     1
2  2  78   F 11.5   1.2    2.0    25     0     25     1
3  3  94   M 10.5   1.5    2.6    46     0     46     1
4  4  68   M 15.2   1.2    1.2    92     0     92     1
5  5  90   F 10.7   0.8    1.0     8     0      8     1
```

- Classic data set
  - One row per subject
  - Separate columns for death and plasma cell malignancy
  - Follow-up continues after PCM

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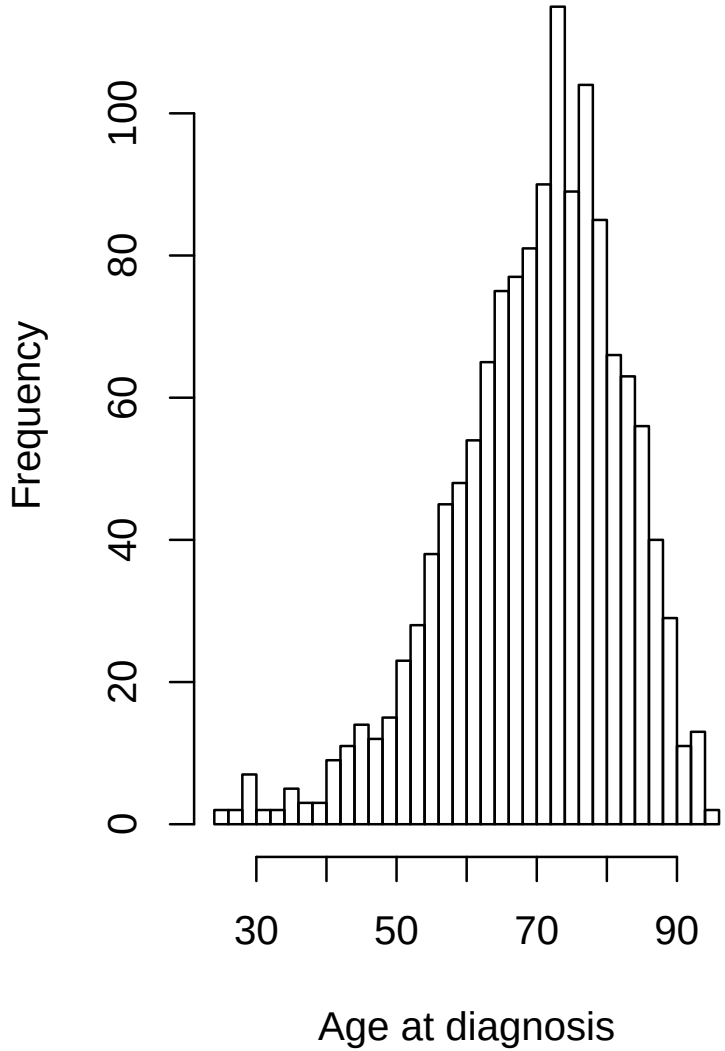
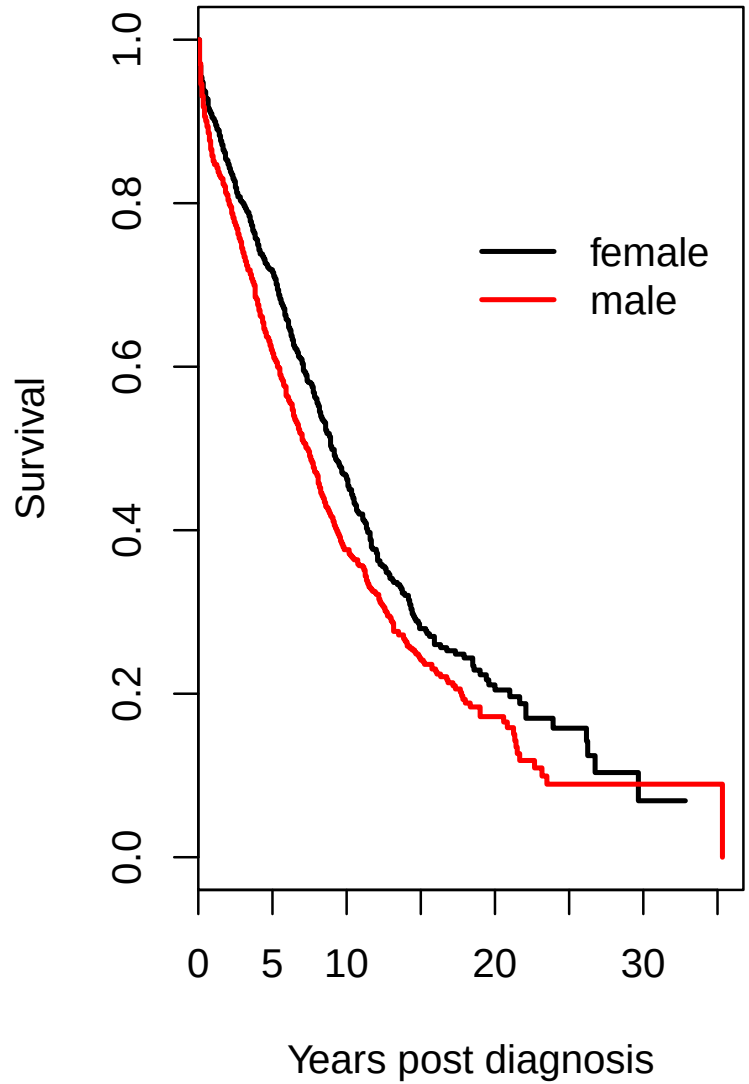

Frequency
0
20
40
60
80
100
30
50
70
90
Age at diagnosis


Survival
0.0
0.2
0.4
0.6
0.8
1.0
female
male
0
5
10
20
30
Years post diagnosis

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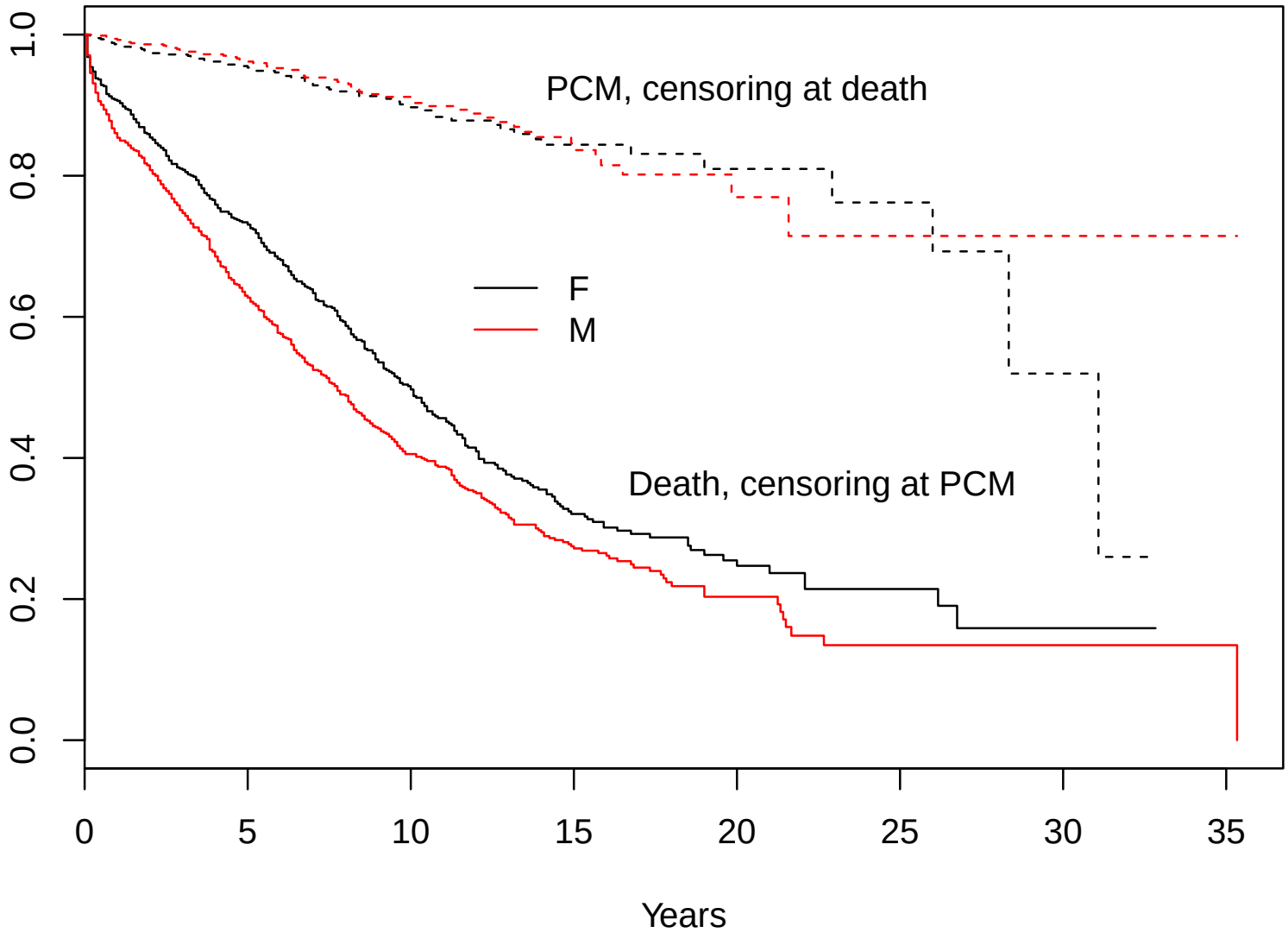
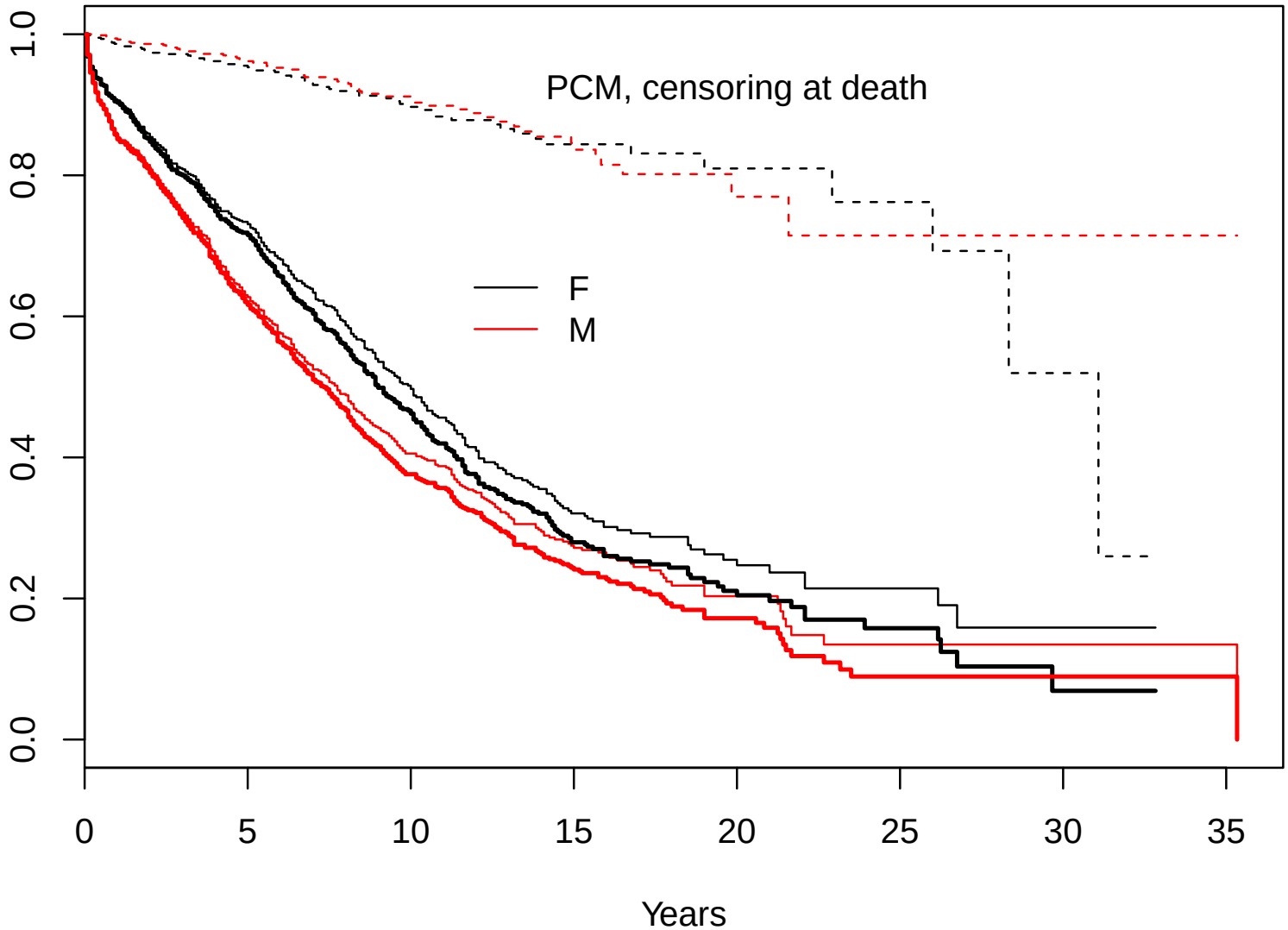
Common analysis




PCM, censoring at death
F
M
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
35
Years

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Competing Risks

- For this illustration we are only interested in the first event for each subject.
- Formally we are treating progression to a plasma cell malignancy (PCM) as an *absorbing state*, i.e., one that subjects never exit.
- The event variable was created as a factor. The first level of the factor must be censoring, which is the status code for those whose follow-up terminated without reaching either endpoint. Codes for the remaining states can be in any order. The labels are arbitrary.
- A simple print of the `mfit2` object shows the order in which the curves will be displayed. This information was used to choose the line types and colors for the curves.
- Curves start at 0.

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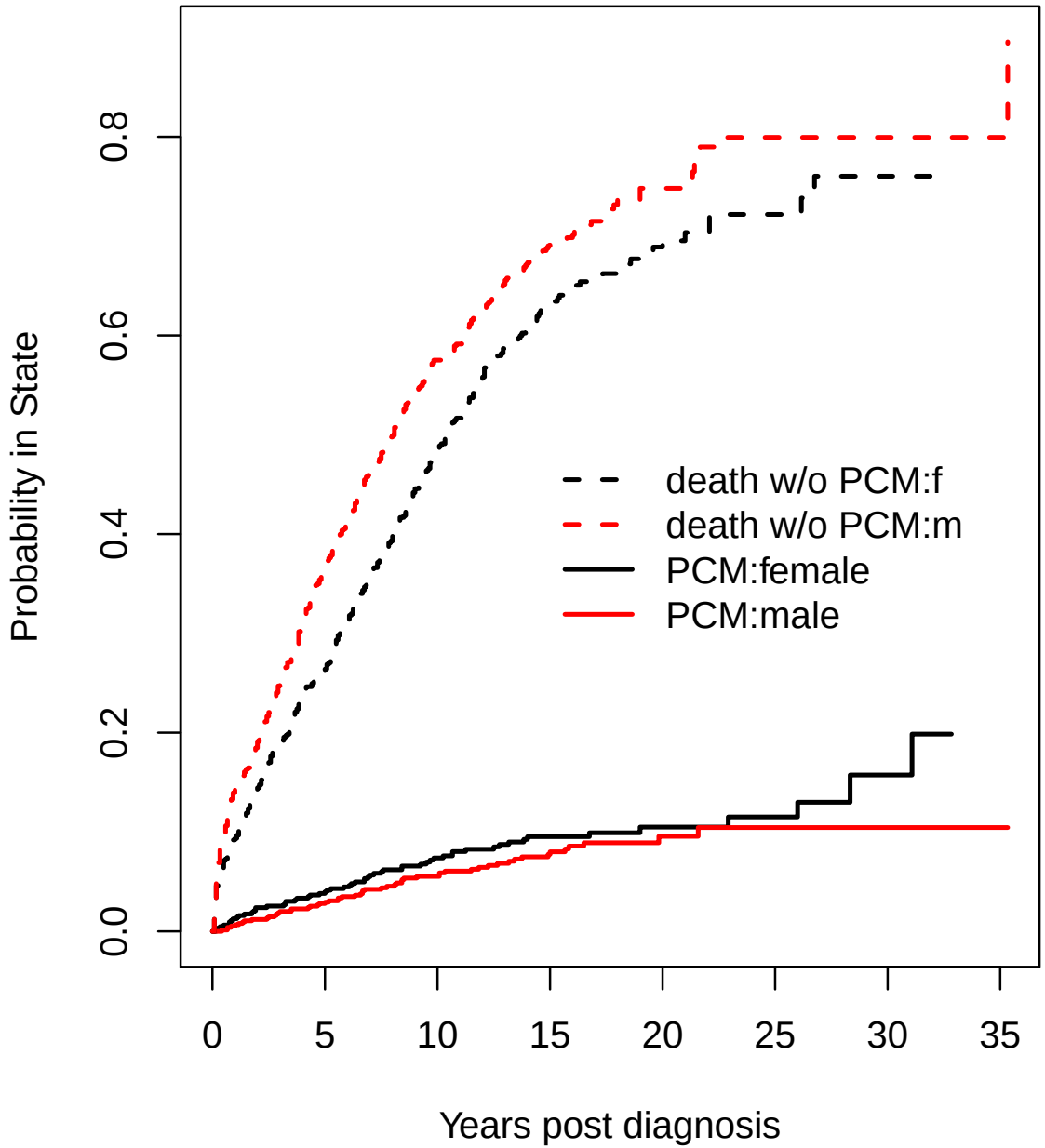
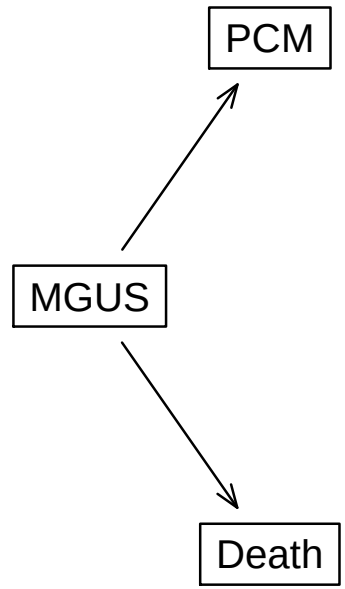
Competing Risk (Aalen-Johansen)





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```
> mfit2 <- survfit(Surv(etime, event) ~ sex, data=mgus2)
> print(mfit2, rmean=240, scale=12)
Call: survfit(formula = Surv(etime, event) ~ sex, data = mg

                n nevent    rmean*
sex=F, pcm    631     59  1.323284
sex=M, pcm    753     56  1.064693
sex=F, death  631    370  8.823108
sex=M, death  753    490 10.260294
sex=F,        631      0  9.853608
sex=M,        753      0  8.675012
   *mean time in state, restricted (max time = 20 )
```

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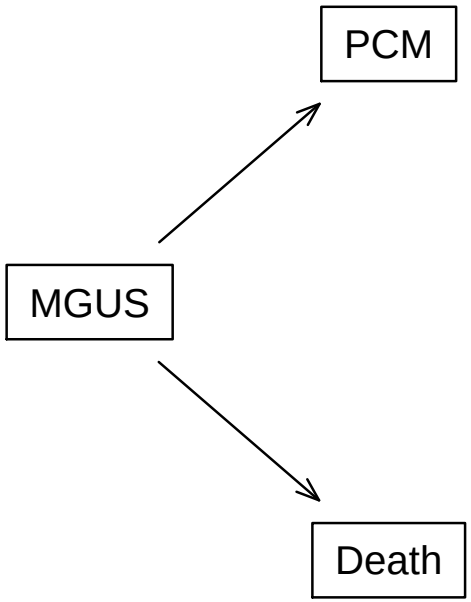
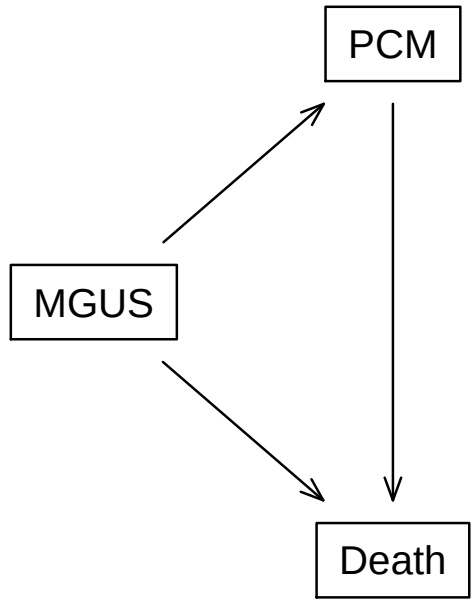
Footnote: Alternate model





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- Left figure: ever PCM and death without PCM
- Right figure: currently in PCM, ever dead
- Same status variable, different data set

Raw data

	id	age	sex	ptime	pstat	futime	death
80	80	80	M	68	0	68	1
81	81	91	F	14	1	21	1
82	82	71	M	65	0	65	1
83	83	77	F	228	1	233	1

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CR data: add two variables

```
   id age sex ptime pstat futime death etime event
80 80  80   M    68     0     68     1    68 death
81 81  91   F    14     1     21     1    14   pcm
82 82  71   M    65     0     65     1    65 death
83 83  77   F   228     1    233     1   228   pcm
```

Figure 2: add lines

```
   id age sex tstart tstop event
81 80  80   M      0    68 death
82 81  91   F      0    14   PCM
83 81  91   F     14    21 death
84 82  71   M      0    65 death
85 83  77   F      0   228   PCM
86 83  77   F    228   233 death
```

- The first version of the data set generated errors.
- 9 subjects have PCM and death declared at the same time.
- Treated as PCM in the CR analysis
- For the multi-state model we need to be explicit
- Push progressions back by .1 month when there is a tie

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- The first version of the data set generated errors.
- 9 subjects have PCM and death declared at the same time.
- Treated as PCM in the CR analysis
- For the multi-state model we need to be explicit
- Push progressions back by .1 month when there is a tie
- Many data sets have case like this.

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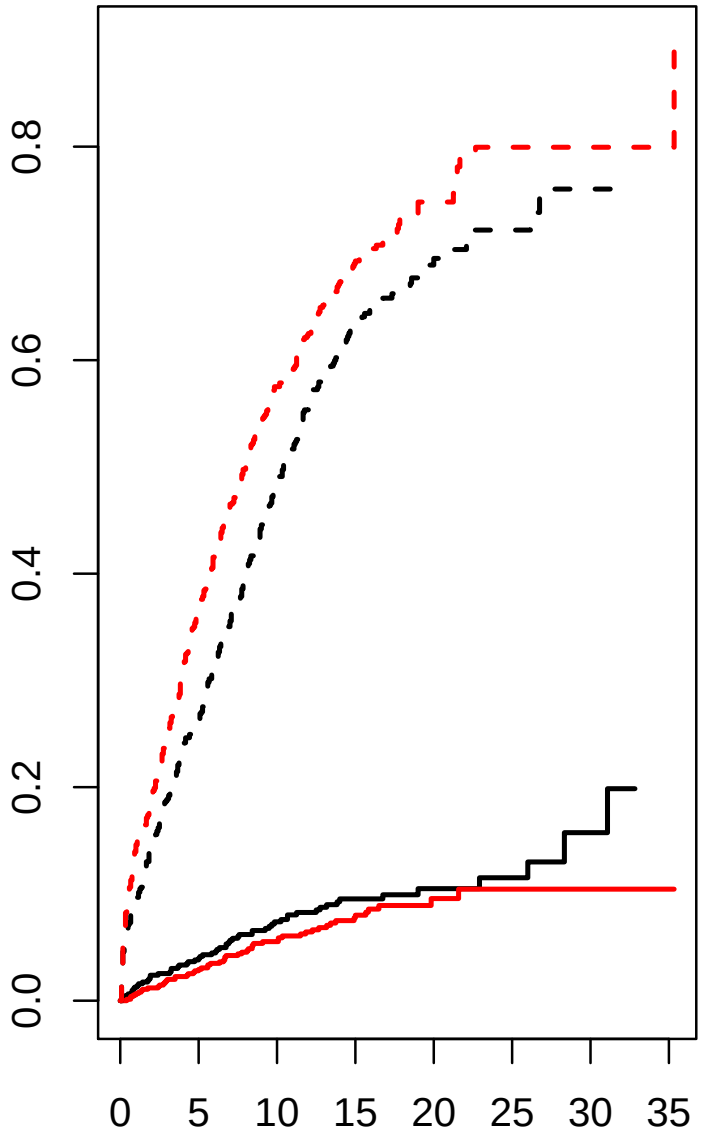
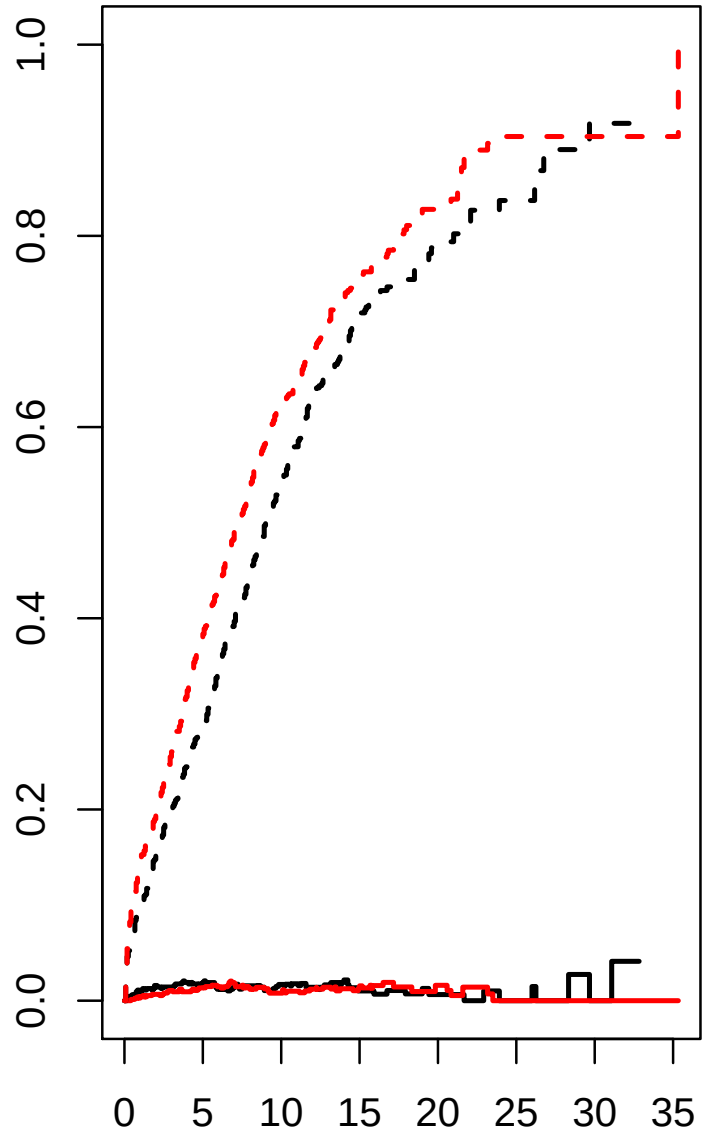

0.0
0.2
0.4
0.6
0.8
0
5
10
15
20
25
30
35


0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
30
35

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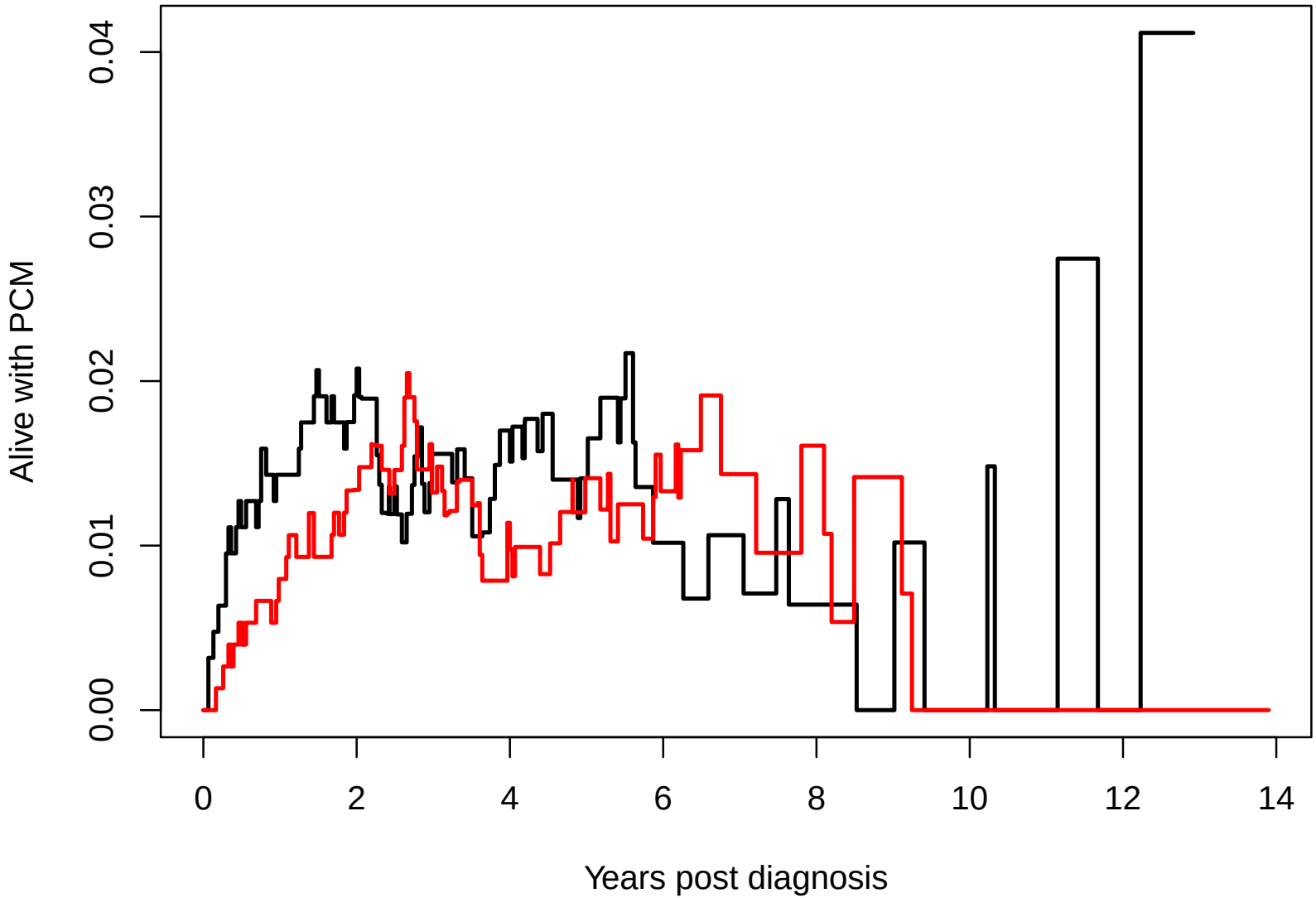
Alive with PCM
0.00
0.01
0.02
0.03
0.04
0
2
4
6
8
10
12
14
Years post diagnosis

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Look at multiple factors

```
> oldage <- (mgus2$age > 70)
> bigm   <- mgus2$mspike > 1
> pfit2 <- survfit(Surv(etime, event) ~ oldage + sex +
                   bigm, data= mgus2)
>
> plot(pfit2, col=1:8, lty=rep(1:2, each=8),
      xscale=12, xlab="Years since MGUS")
```

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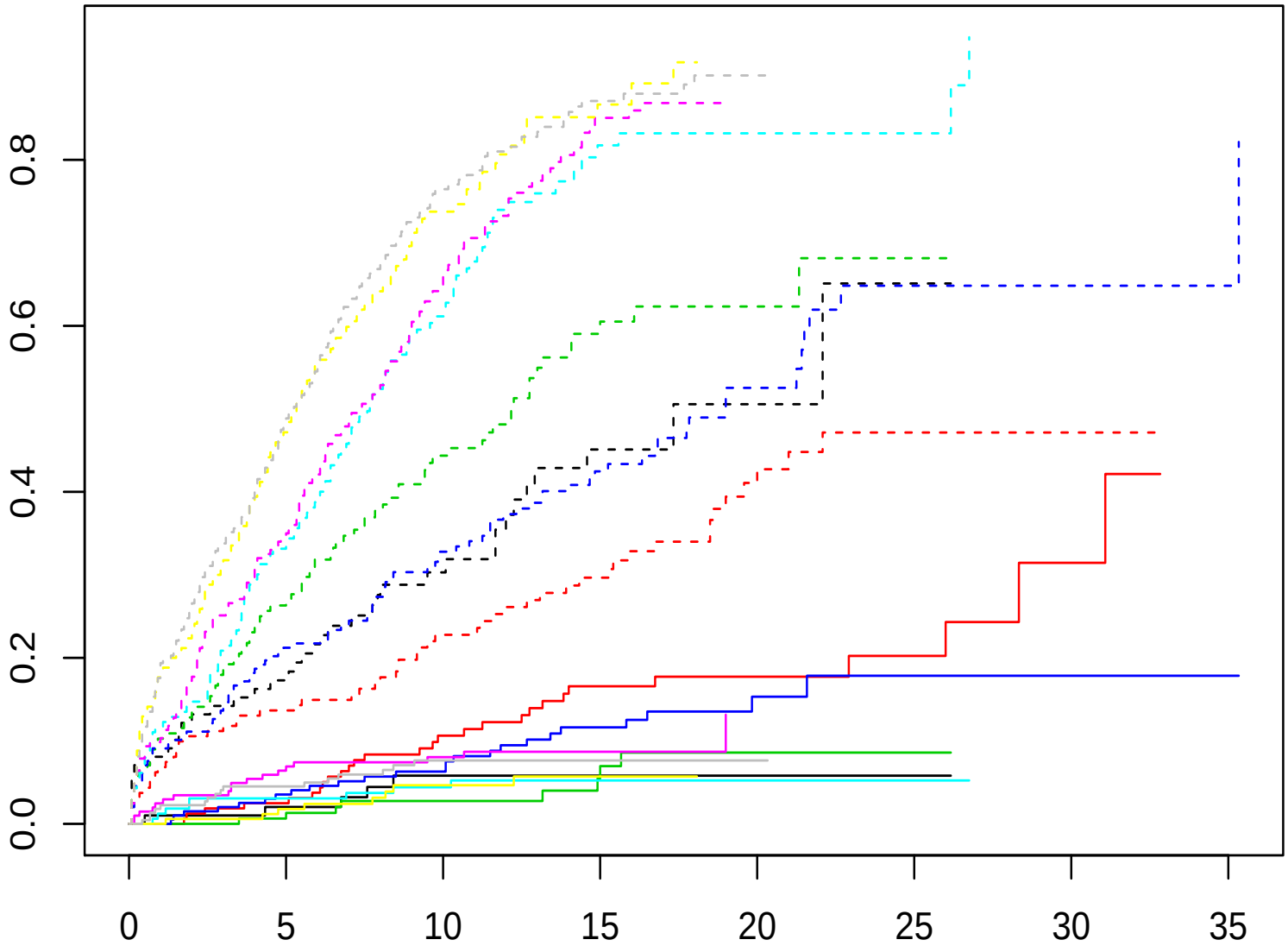
Tangle of yarn plot



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Hazard models

- Model the individual rates $\lambda_{jk}(t)$ from state j to state k
- Separate model for each transition
  - which covariates for each
  - which, if any, coefficients are shared
  - what time scale for each transition (baseline hazard)
  - do any transitions share a baseline
- A given arrow only depends on the starting box and the transitions
  - At risk = in the starting box
  - Event = transition of *this* type, all others are treated as censored

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```
> cfit1 <- coxph(Surv(etime, event=="death") ~ sex + mspike
                 data= mgus2)
> round(summary(cfit1)$coef, 2)
        coef exp(coef) se(coef)     z Pr(>|z|)
sexM    0.22      1.25     0.07  3.19     0.00
mspike -0.14      0.87     0.06 -2.14     0.03
> cfit2 <- coxph(Surv(etime, event=="pcm") ~ sex + mspike,
                 data= mgus2)
> round(summary(cfit2)$coef, 2)
        coef exp(coef) se(coef)     z Pr(>|z|)
sexM   -0.04      0.96     0.19 -0.23     0.82
mspike  0.86      2.37     0.17  5.21     0.00
> quantile(mgus2$mspike, na.rm=TRUE)
  0%  25%  50%  75% 100%
 0.0  0.6  1.2  1.5  3.0
```

Simple event rates

```
> pfit <- pyears(Surv(ptime, pstat) ~ sex, scale=12*100,
                 data=mgus2)
> pfit$event/pfit$pyears
sex
       F        M
1.117354 1.016626
```

- Overall rate is 1% per year for males, 1.1% for females
- In 15 years we would expect 15–16% to progress
  if there were no deaths

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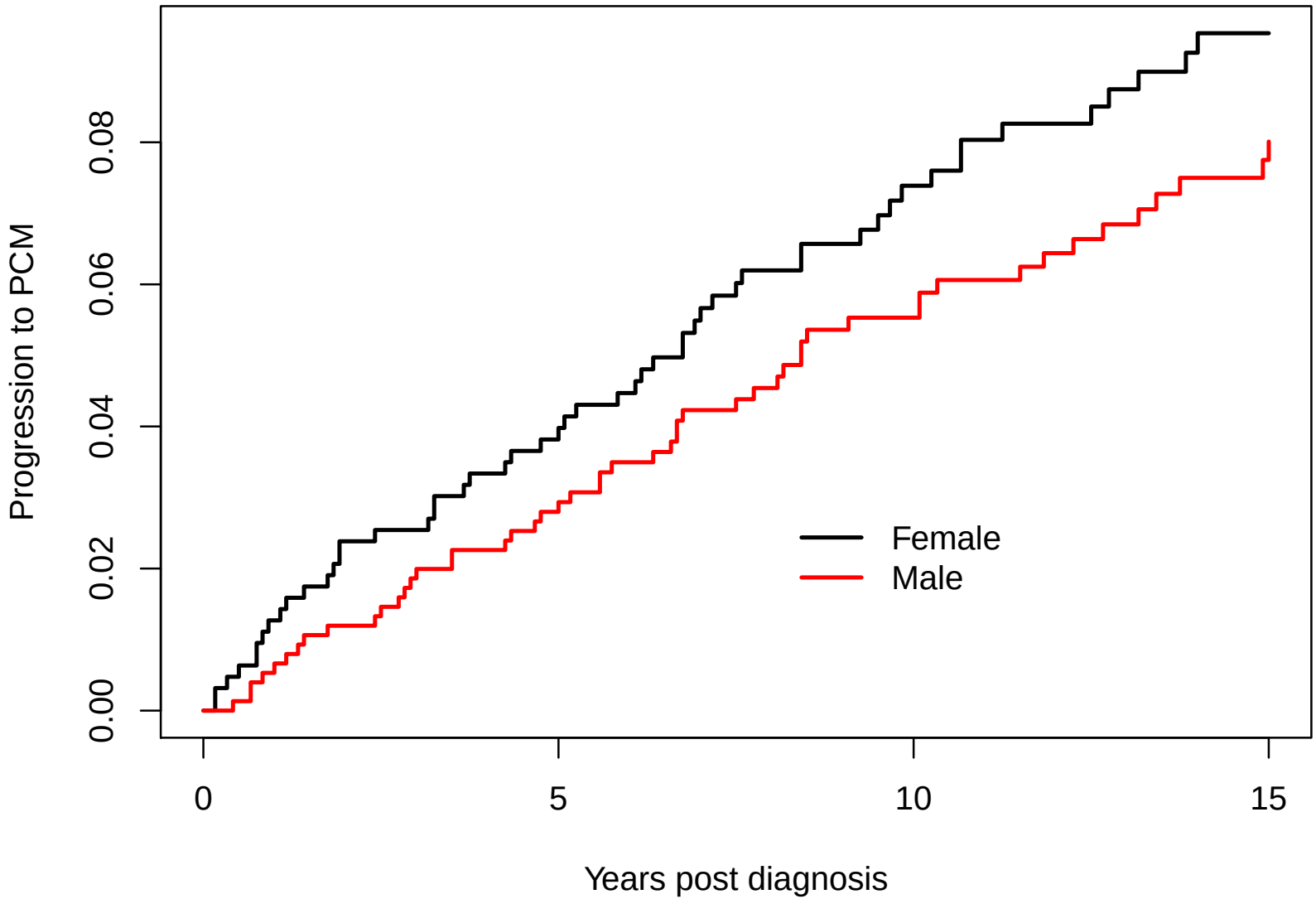
Progression to PCM



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Lesson 1

- Any given rate (arrow) is modeled using that endpoint and ignoring all others (treat them as censored). Individual rates are local.
- The probability of being in any one state (box) depends on *all* the rates. States are global.
  - Sex has no effect on progression to PCM.
  - But females have a higher 15 year risk (9.5 vs 7.5)

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- Any given rate (arrow) is modeled using that endpoint and ignoring all others (treat them as censored). Individual rates are local.
- The probability of being in any one state (box) depends on *all* the rates. States are global.
  - Sex has no effect on progression to PCM.
  - But females have a higher 15 year risk (9.5 vs 7.5)
  - Mean life remaining for this age distribution is 16.5 and 14.4 years, respectively.

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- Underlying biology question: does gender affect the rate of progression?
- Public health question: does gender affect the lifetime risk?
- They have different answers.

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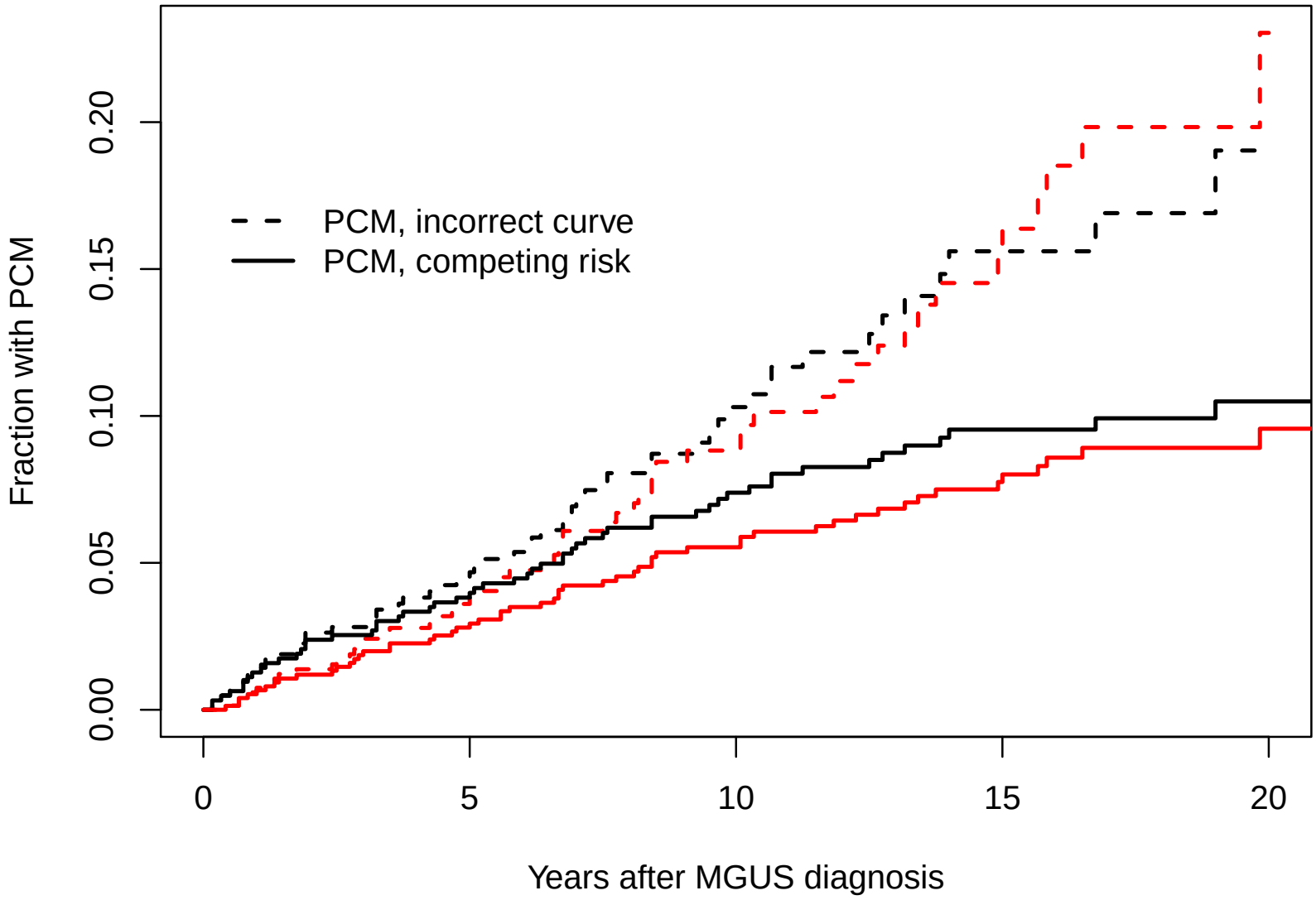
PCM, incorrect curve
PCM, competing risk
Fraction with PCM
0.00
0.05
0.10
0.15
0.20
0
5
10
15
20
Years after MGUS diagnosis

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Consequences of the rates

- Can we predict multivariate outcome from a set of Cox models? Yes.
  - As with all Cox models, prediction must be for some particular person(s).
  - Decision: male/female by age 60/80, with mspike= 1.2
  - Create a 4 observation data set `newdata`

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Consequences of the rates

- Can we predict multivariate outcome from a set of Cox models? Yes.
  - As with all Cox models, prediction must be for some particular person(s).
  - Decision: male/female by age 60/80, with mspike= 1.2
  - Create a 4 observation data set `newdata`
  - Individual curves, from each Cox model alone, are useless; proper curves require *all* the rates.
  - Aalen-Johansen estimator, with $\lambda(t|z)$ as entries.
  - Result is 8 curves: predicted lifetime risk of PCM and of death before PCM, each for m/f at age 60/80.

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$$H = \begin{pmatrix} \lambda_{11}(t) & \lambda_{12}(t) & \lambda_{13}(t) \\ \lambda_{21}(t) & \lambda_{22}(t) & \lambda_{23}(t) \\ \lambda_{31}(t) & \lambda_{32}(t) & \lambda_{33}(t) \end{pmatrix}$$
$$= \begin{pmatrix} * & \lambda_{12}(t) & \lambda_{13}(t) \\ 0 & * & 0 \\ 0 & 0 & * \end{pmatrix}$$

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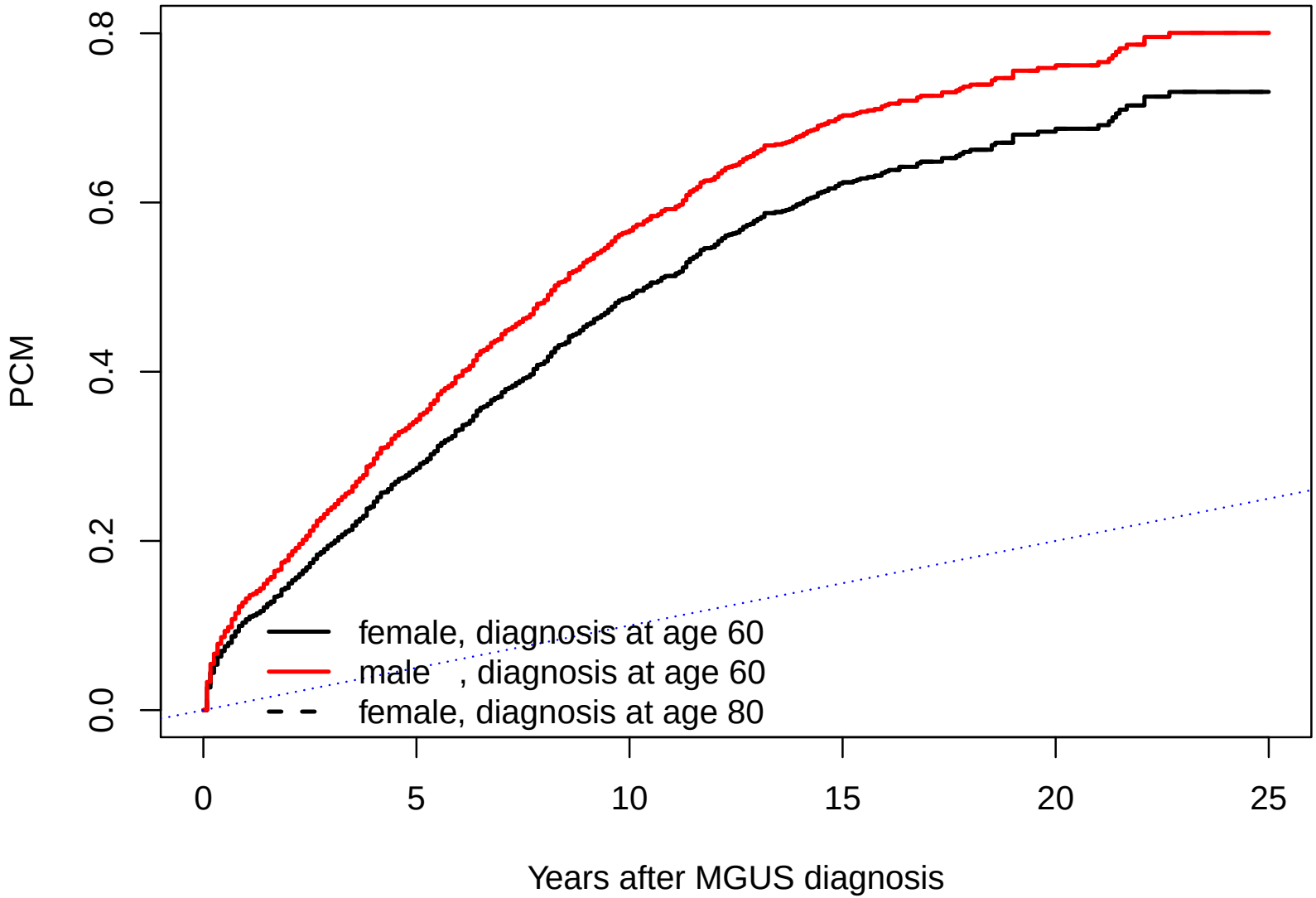
PCM
0.0
0.2
0.4
0.6
0.8
0
5
10
15
20
25
Years after MGUS diagnosis
female, diagnosis at age 60
male , diagnosis at age 60
female, diagnosis at age 80

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Prediction at 25 years

	female	male	delta
diagnosis at age 60	.142	.118	.024
diagnosis at age 80	.086	.060	.026

- 2.5% increase for females
- Not a constant wrt to other covariates, even though the HR for sex is constant within each each of death and PCM. PH for components $\neq$ PH for the composite.
- A good summary is a population average prediction = mean prediction over the all the other covariates.
  - For each combination of age and mspike in the data set
  - Compute the CI curves, tabulate the difference at age 90
  - Bootstrap

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mstate package

- Create a *stacked* data set
  - 1384 obs for the MGUS to PCM transition
  - 1384 obs for the MGUS to death transition
  - 115 obs for the PCM to death transtion (optional)
  - Add `from` and `to` as covariates
  - Each obs has `status` =1 if *this* transition occured
- Create a 3x3 transition matrix
- Fit all the models at once

```
coxph(Surv(time, status)   (age + sex)*
strata(from, to), ...)
```

- The `mfit` command will create the AJ curves
  - includes variance/covariace

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Fine-Gray model

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Fine-Gray model

- Lament (wrt hazard models)
  - "It's too hard!"
  - "I only want the overall effect"
  - "What's the p-value?"
  - "I want my hazard ratios back"
- Solution: Pretend it's simple
  - Turn the problem into a set of two-state survival problems
  - Solve each separately

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Problem

We have met the enemy and he is us. Pogo

- Statisticians and their customers are addicted to a 1 number summary
- Reality is rarely so simple
- Usual approach is to close our eyes and pretend
  - linear model: $E(y) = \beta_0 + \beta_1 x_1 + \ldots$
  - logistic: $E(y) = f(\beta_0 + \beta_1 x_1 + \ldots)$
  - Cox: $\log(\lambda(t)) = \beta_0(t) + \beta_1 x_1 + \ldots$
- This is much harder with multi-state data.

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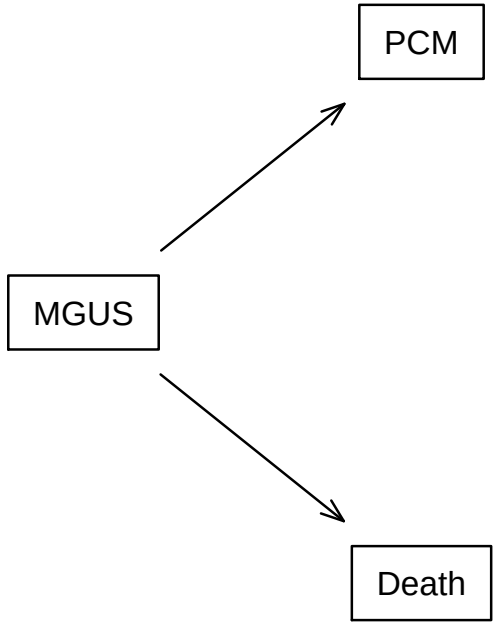
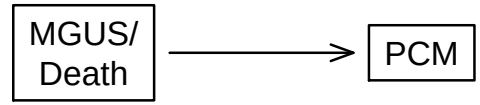
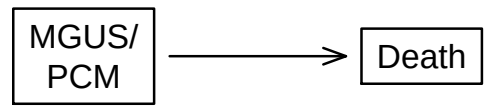

PCM
MGUS
Death


MGUS/
Death
PCM


MGUS/
PCM
Death

Cox model

In a Poisson model there is a relationship between the cumulative hazard λt and the CDF:

$$P(X < t) = \exp(-\lambda t)$$

An ordinary Cox model has the same relationship.

$$\begin{aligned}
\lambda(t) &= \lambda_0(t) \exp(X\beta) \\
S(t) &= \exp\left[- \int_0^t \Lambda_0(t) \exp(X\beta) \right] \\
&= p_1(t)
\end{aligned}$$

where state 1 is the entry state. It is somewhat odd that there are simple expressions for the hazard of an *having* an event at t and the cumulative probability of *not having* that event by time t.

Fine-Gray model

Rewrite as

$$
\begin{aligned}
e^{-\Lambda(t)} &= S(t) \\
1 - p_2(t) & \\
\log(-\log(1 - p_2(t))) &= B_0(t) + \beta_1 x_1 + \ldots \\
B_0(t) &= \int_0^t \beta_0(s) ds
\end{aligned}
$$

Looks like complimentary log-log regression

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Fine-Gray

Ordinary Cox

$$1 - p_2(t) = p_1(t) = \exp\left[-\int_0^t \Lambda_0(t)\exp(X\beta)\right]$$

The Fine-Gray model assumes that

$$\begin{aligned} 1 - p_j(t) &= \mathrm{P}(\text{has not yet had event type } j) \\ &= \exp\left[-\int_0^t \Psi_0(t)\exp(X\beta)\right] \end{aligned}$$

where Ψ is the cumulative "sub-distribution hazard".
Why?

- If such a model holds, then β has a simple interpretation wrt actually attaining a given outcome, independent of the others

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Fine-Gray

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where Ψ is the cumulative "sub-distribution hazard".
Why?

- If such a model holds, then β has a simple interpretation wrt actually attaining a given outcome, independent of the others
- *If*

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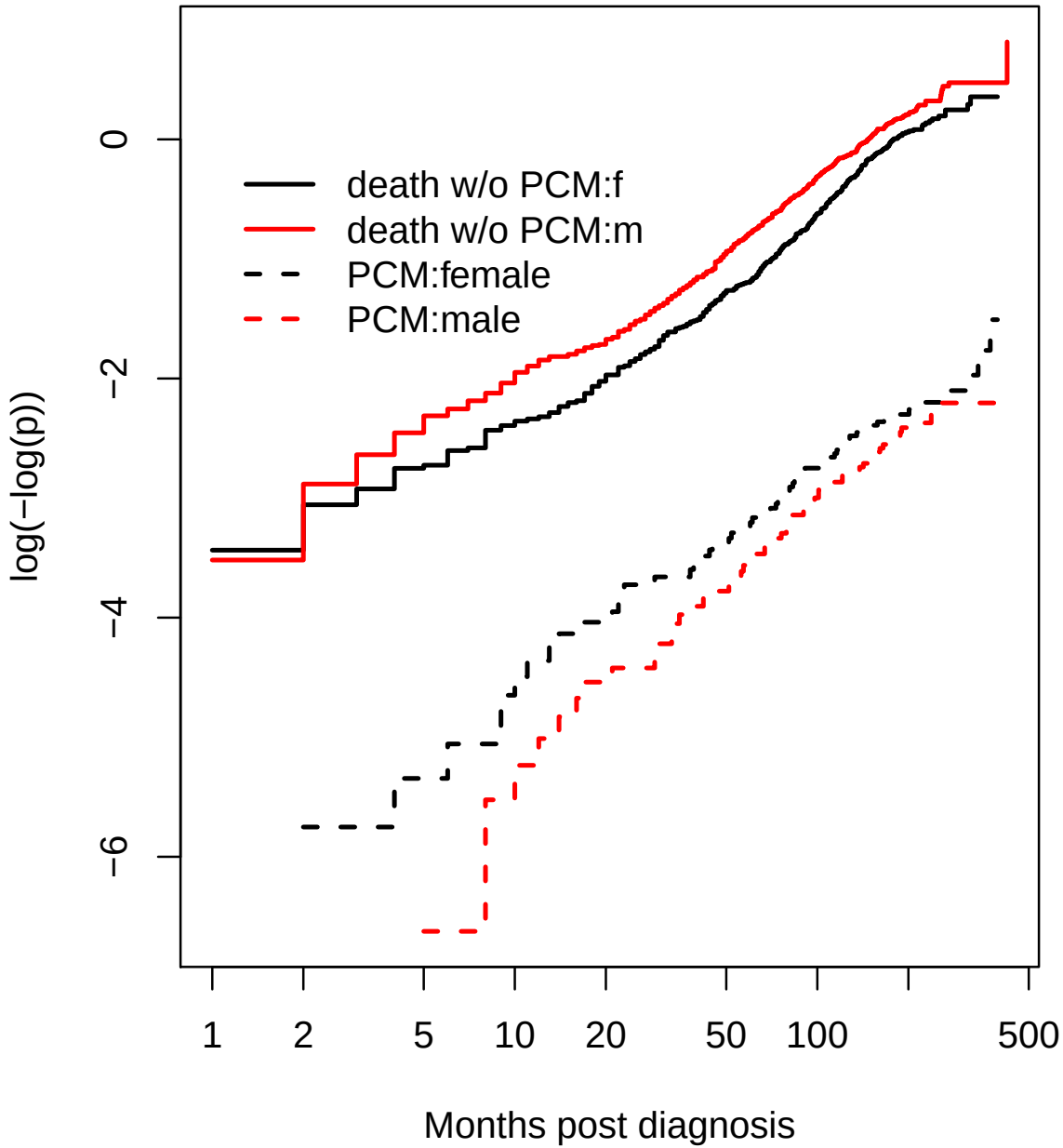
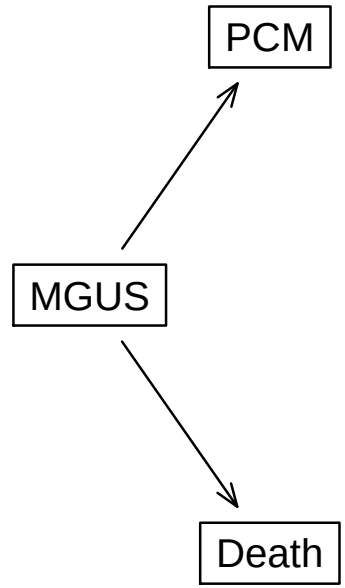
FG works on these curves





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Computation

- The Fine-Gray model can be computed by
  - Create a special dataset for each outcome.
    - Subjects who experience another outcome are extended out in time, with decreasing weight
    - The status variable in the new data is 0/1.
  - Fit a Cox model to the new data, with the case weights.
- Normal model checking can be applied.
- Ordinary post-coxph survival curves can be computed, which will be the FG estimates.
- Fine and Gray suggest a robust variance, Geskus disagrees.

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```
> fdata1 <- finegray(Surv(etime, event) ~ id + age + sex + mspike,
                     etype = "pcm", data= mgus2)
> fdata1[1:4,]
  id age sex mspike fgstart fgstop fgstatus      fgwt
1  1  88   F    0.5       0     35        0 1.0000000
2  1  88   F    0.5      35     44        0 0.9990449
3  1  88   F    0.5      44     47        0 0.9980368
4  1  88   F    0.5      48     52        0 0.9959629
> #
> dim(mgus2)
[1] 1384   10
> dim(fdata1)
[1] 41775     8
> #
> fgfit1 <- coxph(Surv(fgstart, fgstop, fgstatus) ~ age + sex + mspike,
                  weight=fgwt, data= fdata1)
```

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Fits

	Hazard ratio		
	age (decades)	sex (M)	serum M-spike
Cox, PCM	1.18	0.99	2.42
Fine-Gray, PCM	0.84	0.81	2.43
Cox, death	1.92	1.48	0.94
Fine-Gray, death	1.81	1.45	0.86

The raw estimates of PCM risk at 15 years were 9.5 and 8 percent for females and males, respectively, a ratio of 0.84.

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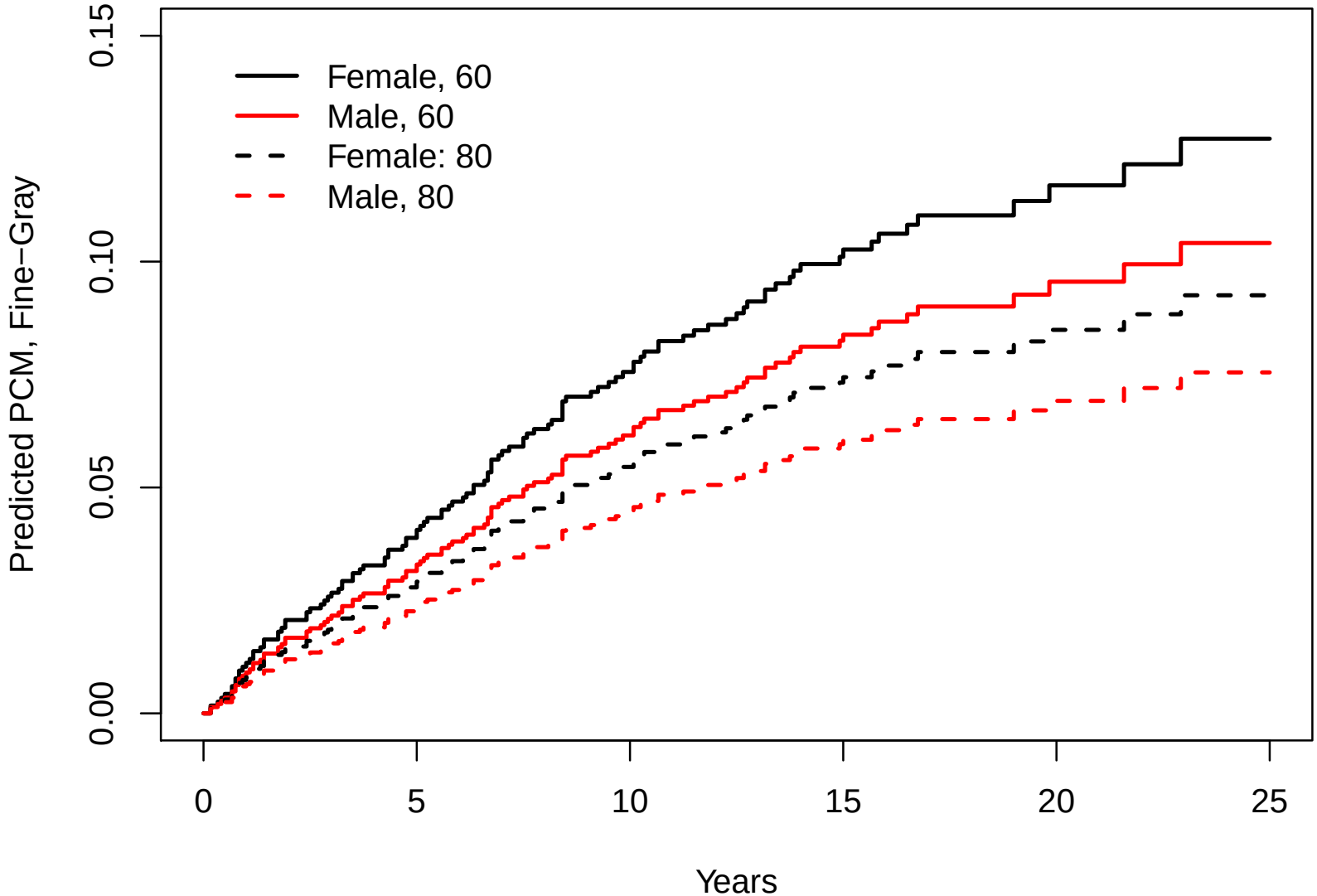
Predicted outcome



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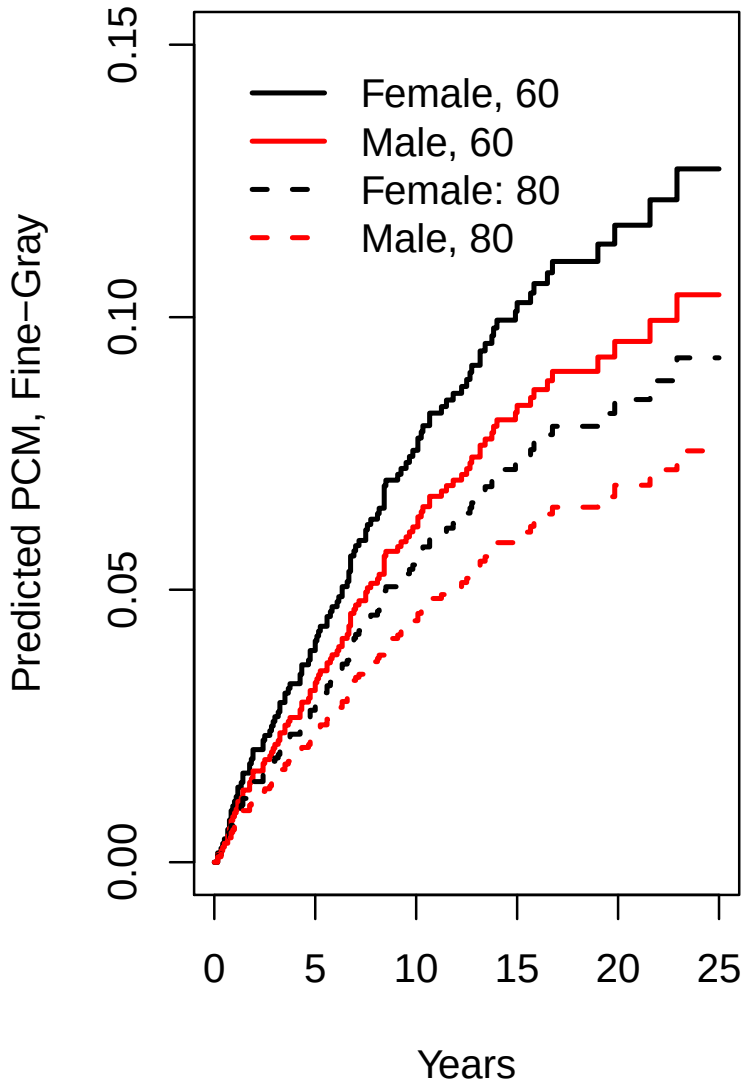
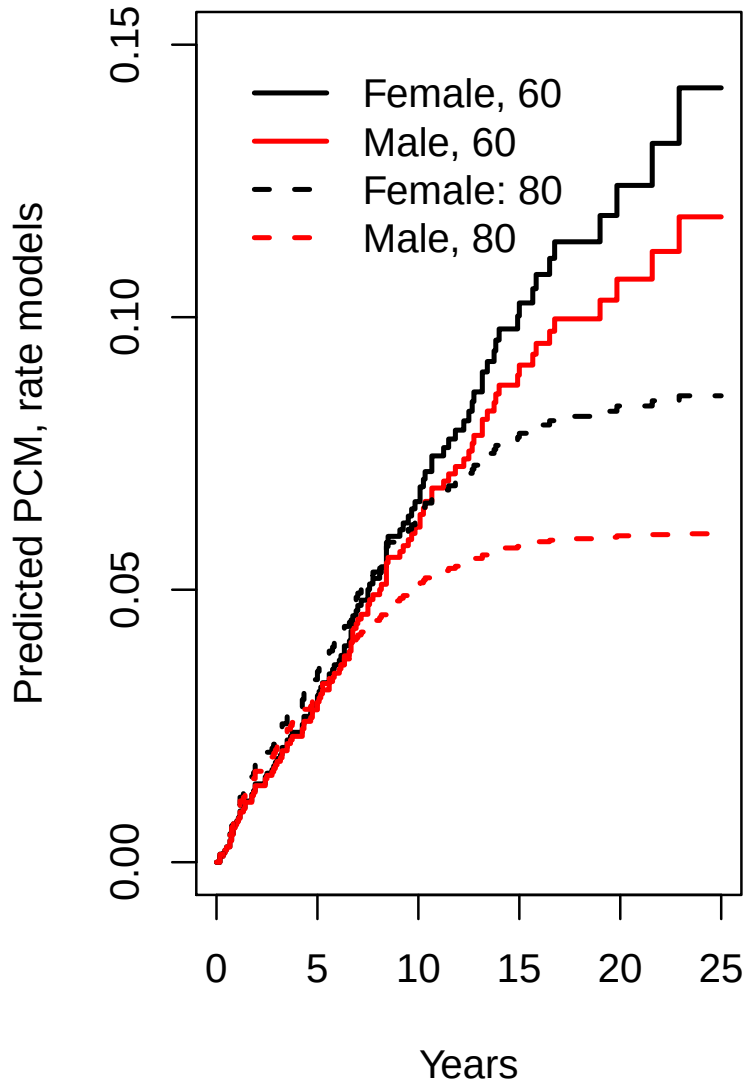

Predicted PCM, Fine−Gray
0.00
0.05
0.10
0.15
0
5
10
15
20
25
Years
Female, 60
Male, 60
Female: 80
Male, 80


Predicted PCM, rate models
0.00
0.05
0.10
0.15
0
5
10
15
20
25
Years
Female, 60
Male, 60
Female: 80
Male, 80

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Which one is right?

- Compare the predictions to the raw data using population averages (direct adjusted survival curves).
- Total
  1. For all n=1384 subjects in the data set get a predicted survival under the FG model
  2. Average the survival curves.
  3. Plot along with the AJ estimate from raw data.
- Within ages: split the data at age 72 (median), repeat for each half separately.

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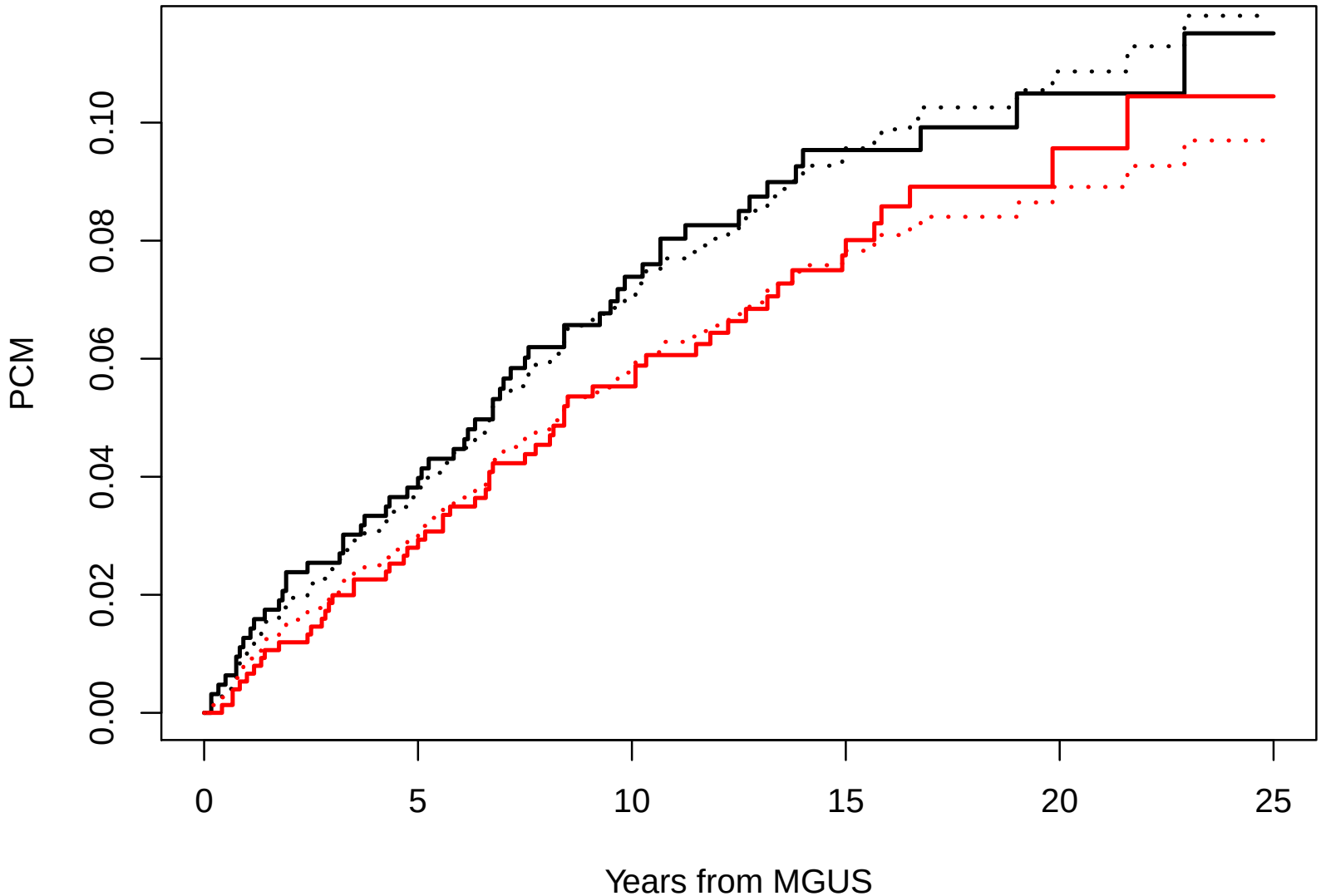
Direct adjusted curves, total



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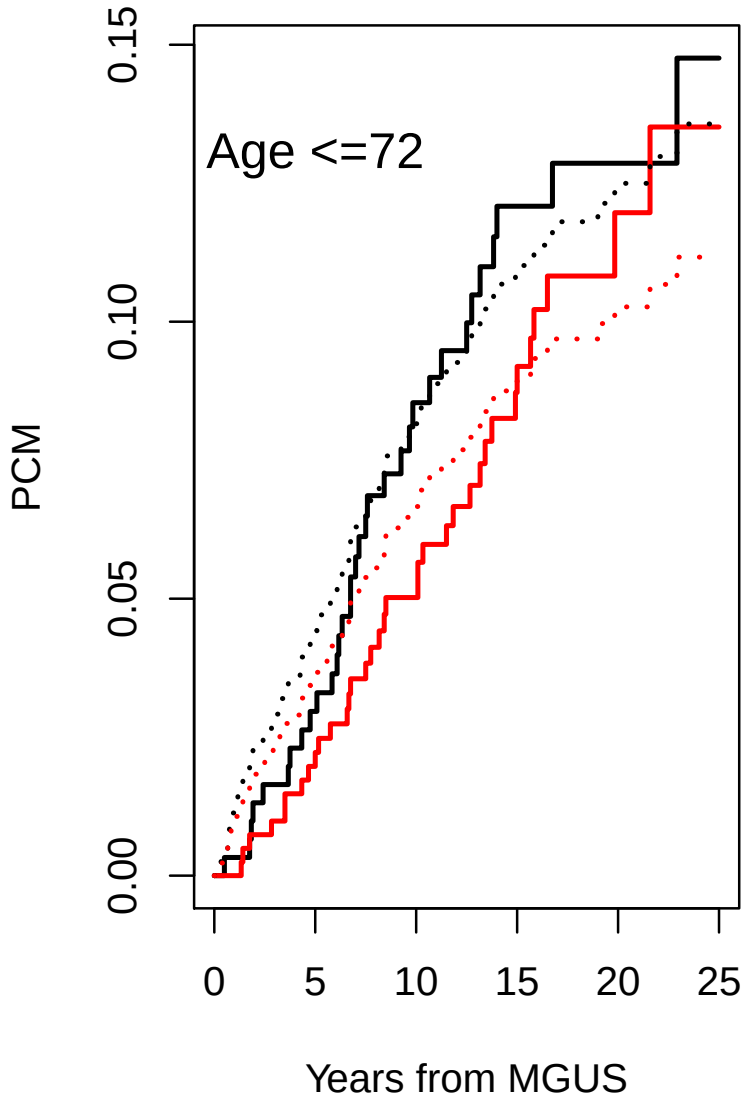
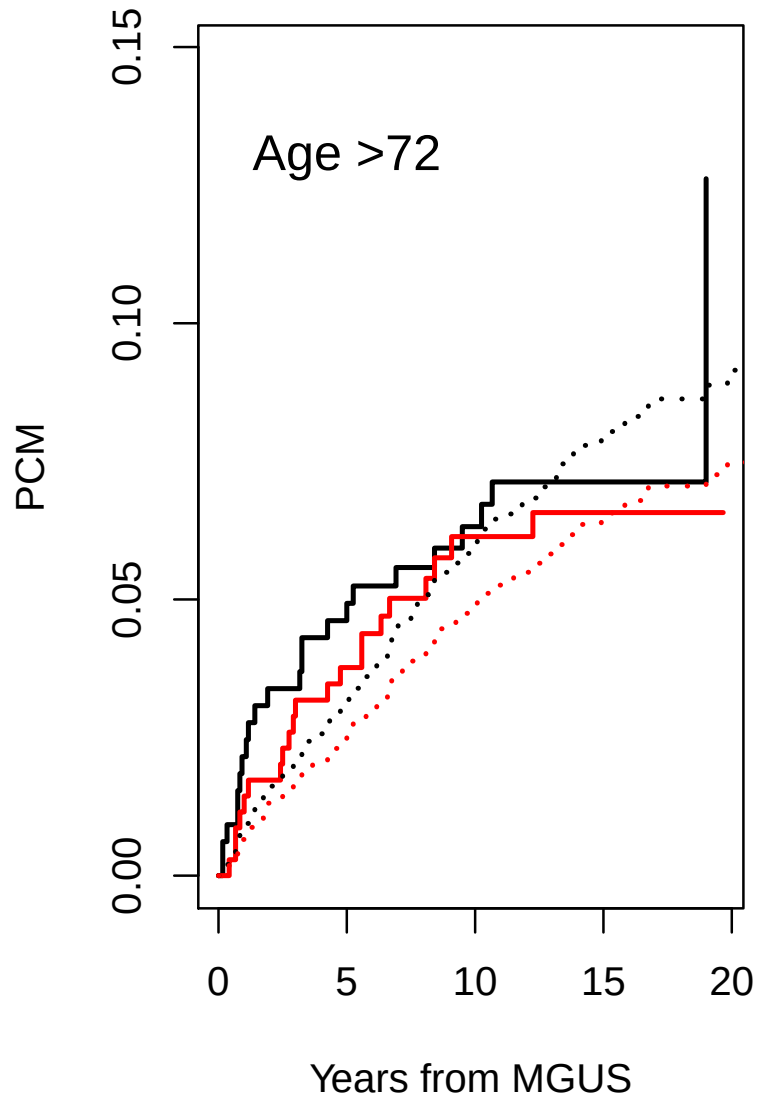
Direct adjusted curves, by age





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Assumptions

- The risk fits assume a Cox model with linear age and mspike effects, additivity, and proportional hazards.
  For both PCM and death risks, but separately.
- The Fine-Gray fits assume a Cox model with linear age and mspike effects, additivity, and proportional hazards.
  For the subdistribution PCM and subdistribution death effects.
- They can't both be true.

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Assumptions

- The risk fits assume a Cox model with linear age and mspike effects, additivity, and proportional hazards.
  For both PCM and death risks, but separately.
- The Fine-Gray fits assume a Cox model with linear age and mspike effects, additivity, and proportional hazards.
  For the subdistribution PCM and subdistribution death effects.
- They can't both be true.
- Model checking is imperative.

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Testing PH

```
> cox.zph(cfit1)
           rho  chisq     p
age    -0.1736 2.3510 0.125
sexM    0.0283 0.0918 0.762
mspike -0.0186 0.0423 0.837
GLOBAL      NA 2.5729 0.462
> #
> cox.zph(fgfit1)
           rho   chisq        p
age    -0.5306 20.9939 4.61e-06
sexM    0.0215  0.0528 8.18e-01
mspike -0.0267  0.0788 7.79e-01
GLOBAL      NA 21.3108 9.07e-05
```

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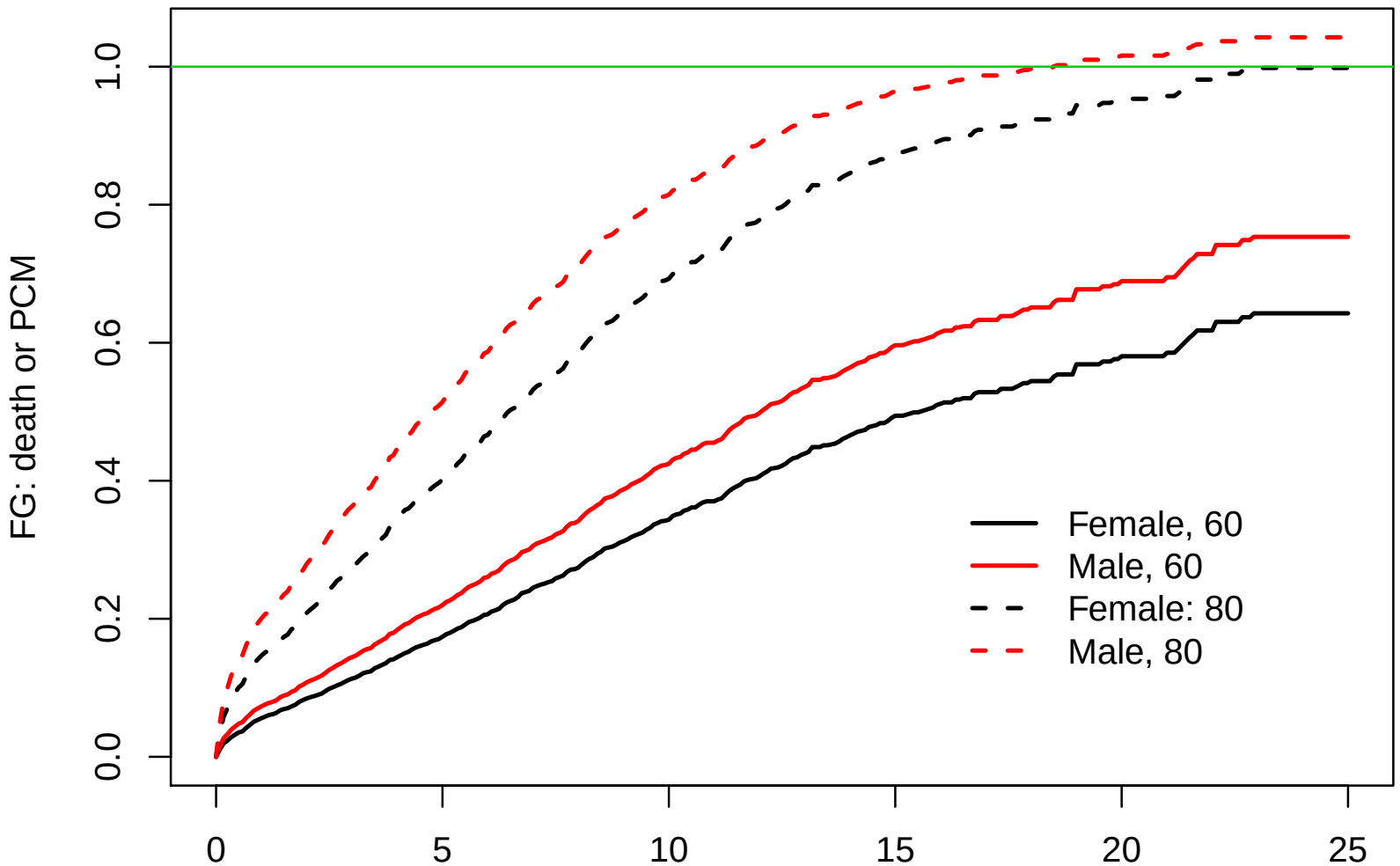
- Look at the predicted fraction who are still endpoint free.
- This is a natural part of the AJ estimate.
- The two FG estimates are separate computations; add them.



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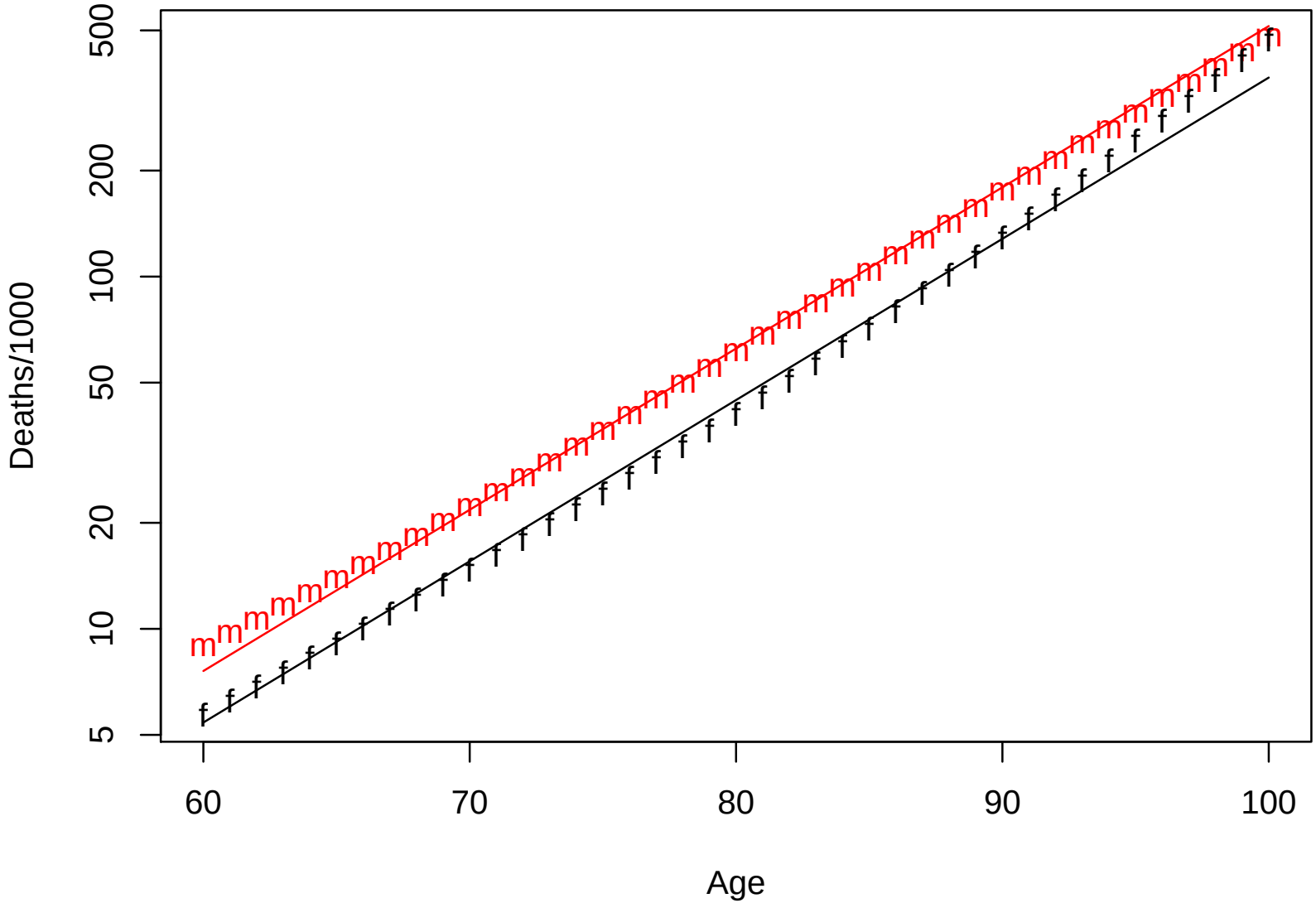
What would an FH hazard look like?



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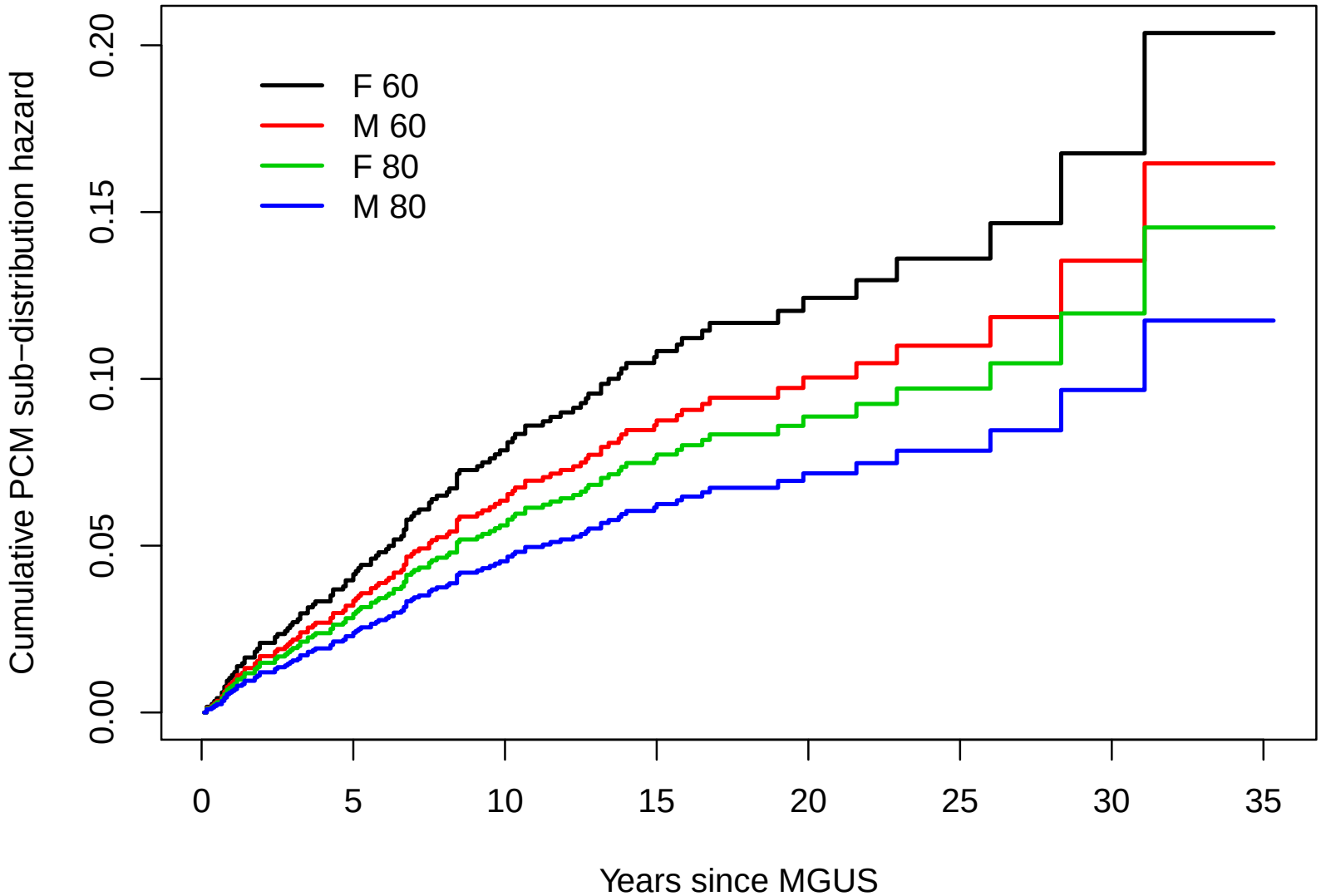
F 60
M 60
F 80
M 80
Cumulative PCM sub−distribution hazard
0.00
0.05
0.10
0.15
0.20
0
5
10
15
20
25
30
35
Years since MGUS

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Formula 5.56 of Beyersmann, Allignol, and Schumacher

$$\alpha_1(t) = \frac{\lambda_1(t)\exp\left(-\Lambda_1(t) + A_2(t)\right)}{1 - \int_1^t \lambda_1(u)\exp\left(-\Lambda_1(u) + A_2(u)\right) du}$$

- $\alpha_1, \alpha_2 =$ hazard for PCM and death
- $\lambda_1 =$ subdistribution hazard for PCM

$$\alpha_2(t) = \exp(-11.5 + .105(a + t) + .37m$$
$$A_2(t) = \exp(-11.5 + .37m + .105a)\left(\exp(.105t) - 1\right)/.105$$

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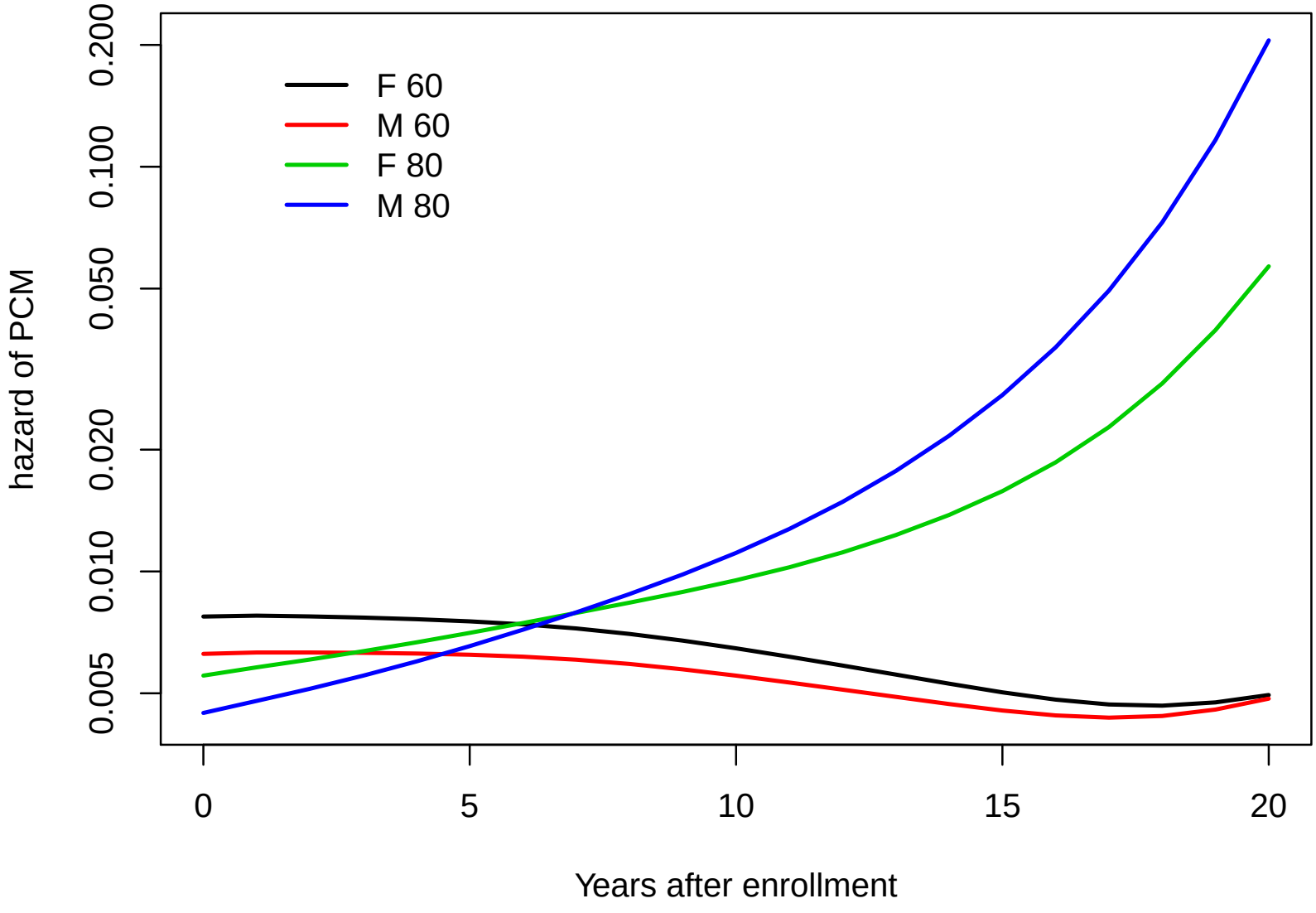
F 60
M 60
F 80
M 80
hazard of PCM
0.005
0.010
0.020
0.050
0.100
0.200
0
5
10
15
20
Years after enrollment

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Why the simple model fails for multi-state data

- Hazards are non-linear
  1. In actuality there are multiple hazard operating for a subject, each with its own covariates

$$\lambda(t) = \lambda_1(t)e^{X\beta} + \lambda_2(t)e^{Z\gamma} + \lambda_3(t)e^{W\psi} + \ldots$$

  2. PH is a model for $\log(\lambda)$, which does not add nicely. Multi-hazards don't collapse to a single PH equation.
  3. The hazard for a heterogeneous collection of subjects is not the average of their hazards.
- Ordinary modeling issues are more acute
  1. Proportional hazards rarely holds over long time periods
  2. Non-linearity and interactions will often be substantial
  3. Time dependent covariates are common and with particular opportunities for misuse
  4. Episodic follow-up processes.
  5. Informative censoring
- Model checks are imperative

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Fine-Gray

- The model often doesn't fit
  - Failure of PH on this scale
  - Particularly with long follow-up
  - Does not extend to other multi-state models
- Wrong interpretation
  - HR of .8 for sex; PCM is then interpreted as females have a higher rate, i.e., different biology.
  - We treat it as though it were a HR on one of the arrows
- Odd
  - Rate model is focused on events/(# at risk for the event)
  - FH is focused on events/(# who have not yet had the event) over time the denominator has more and more subjects who can never have the event
  - There is no obvious biological story that will act this way.

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  - FH is focused on events/(# who have not yet had the event) over time the denominator has more and more subjects who can never have the event
  - There is no obvious biological story that will act this way.
- However
  - If the fraction with no endpoint is $> 80\%$ the fit will often be "okay"

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Survival of the FG model?

- Has a 18 year lead on using a rate model + $p(t)$
- It takes us 20 years for statisticians to catch on
- In the mind of many researchers FG is *the* way to deal with CR.
- FG is in R, Stata, and even SAS

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Survival of the FG model?

- Has a 18 year lead on using a rate model + $p(t)$
- It takes us 20 years for statisticians to catch on
- In the mind of many researchers FG is *the* way to deal with CR.
- FG is in R, Stata, and even SAS

Overall, SAS is about 11 years behind R and S-Plus in statistical capabilities (last year it was about 10 years behind) in my estimation.
– Frank Harrell (SAS User, 1969-1991) R-help (September 2003)

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Multiple disease states

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NAFLD

- A. Allen, Non-alcoholic fatty liver disease incidence and impact on metabolic burden and death, a 20 year community study. Hepatology 2018, 67:1726–1736.
- The prevalence of non-alcoholic fatty liver disease (NASH) has risen to 24%.
- Now the most common cause of chronic liver disease.
- Diagnosed with abdominal MRI.
- NASH = NAFLD + inflammation requires biopsy for diagnosis.

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Study

- All NAFLD diagnosis from 1997 to 2014 in Olmsted County, Minnesota.
- Utilize the Rochester Epidemiology Project
- One year delay.
- 4 controls matched on age and sex, then followed forward until the analysis date.

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Study

- All NAFLD diagnosis from 1997 to 2014 in Olmsted County, Minnesota.
- Utilize the Rochester Epidemiology Project
- One year delay.
- 4 controls matched on age and sex, then followed forward until the analysis date.
- 3864 cases of NAFLD and 14016 controls, 331 overlap.

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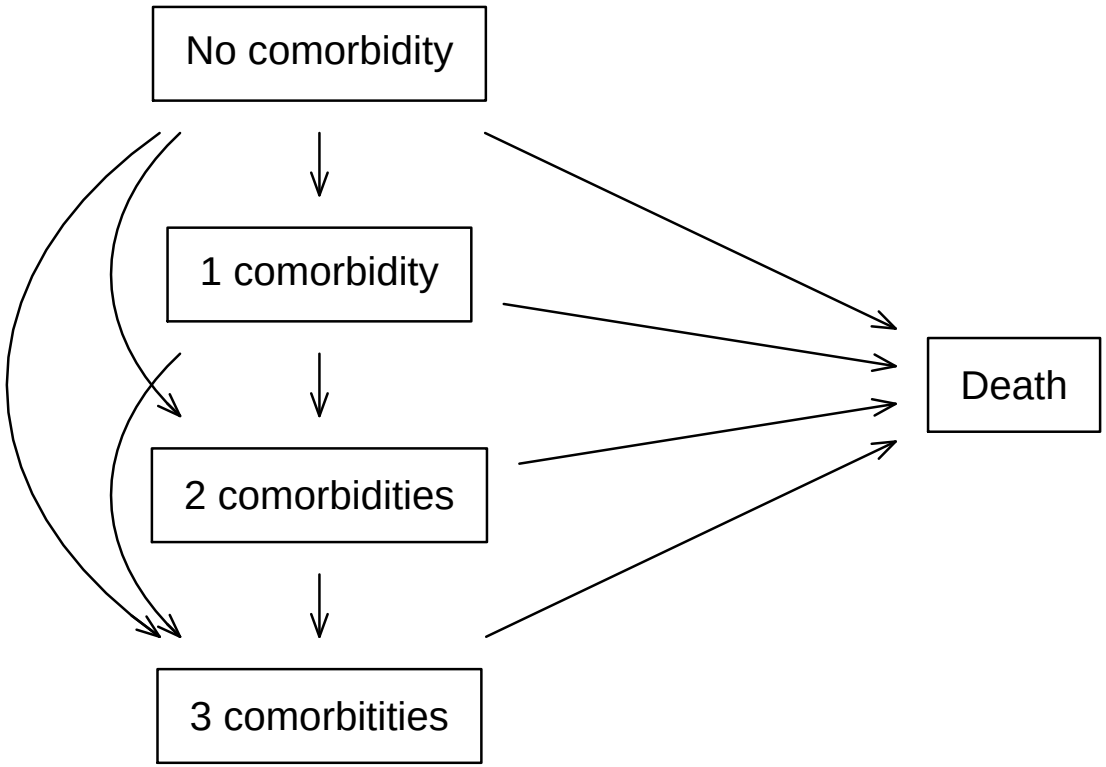
Target



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Data

- `nafld1`: One observation per subject. Baseline covariates plus follow-up time and death.
- `nafld2`: Variables of id, days, test, and value. Contains selected tests and clinical observations.
- `nafld3`: Variables of id, days, and event type. One observation for each outcome: occurrence of NASH, hypertension, diabetes, etc.
- To anonomize patients, all dates have been replaced with "days since first enrollment".

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Data

- Metabolic comorbidities are diabetes, hypertension, and dyslipidemia
- Focus on a model with 0, 1, 2, 3, of these + death
- The real work is in building and checking a data set, the fits will be easy.

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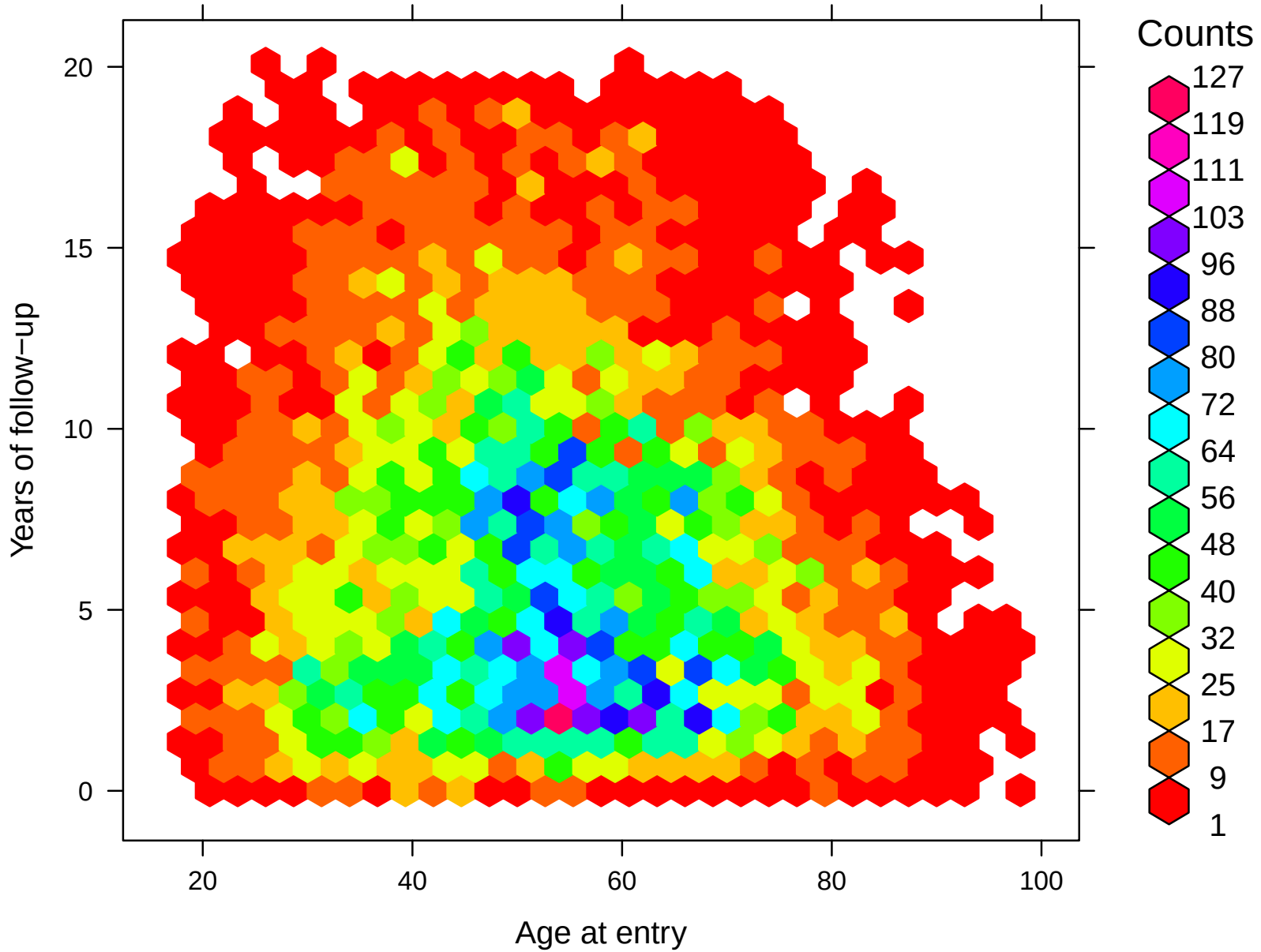
Counts
127
119
111
103
96
88
80
72
64
56
48
40
32
25
17
9
1
Years of follow−up
0
5
10
15
20
Age at entry
20
40
60
80
100

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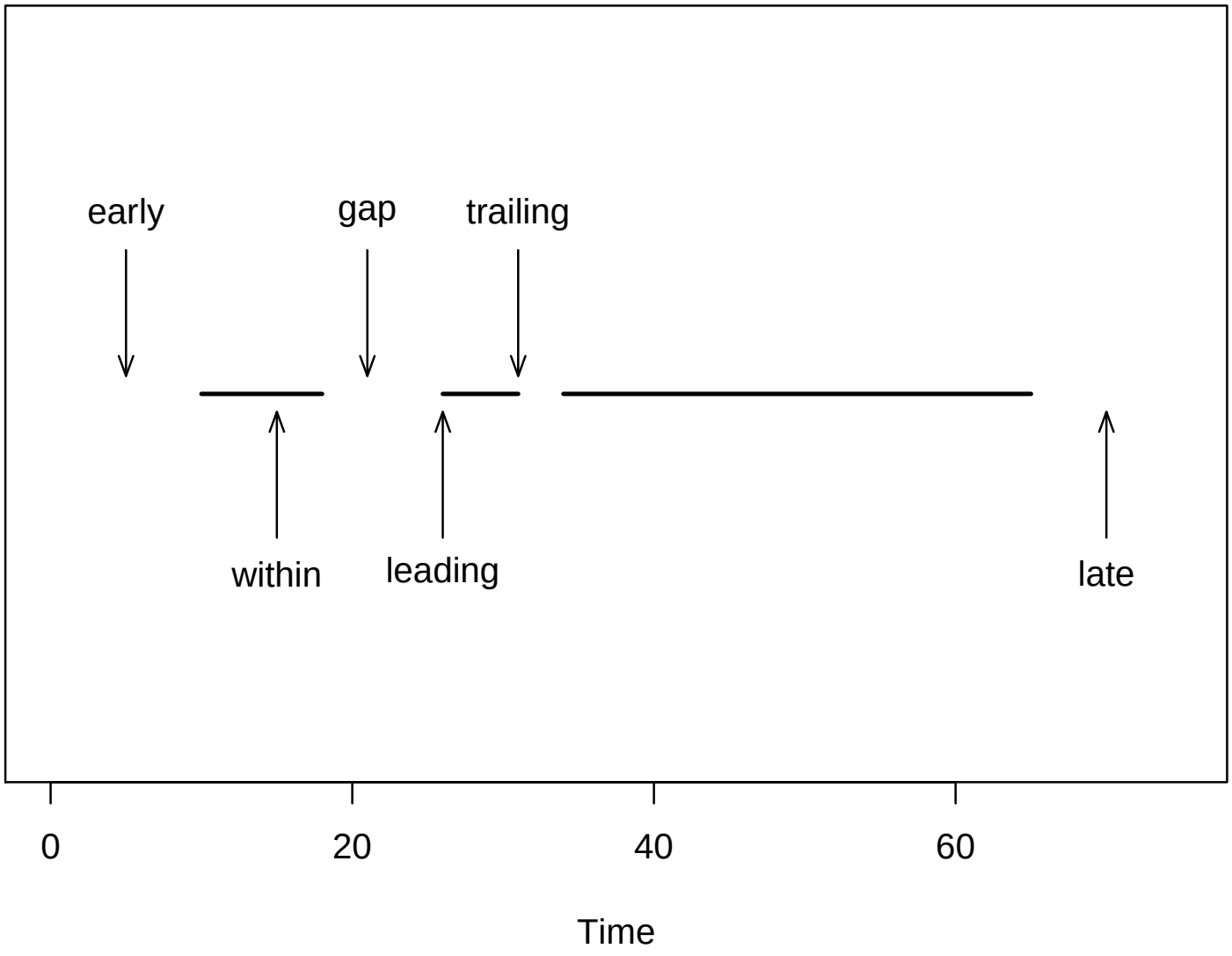
tmerge



R code

```
> keep <- c("id", "age", "male", "bmi", "ntime")
> data1 <- tmerge(nafld1[, keep], nafld1, id,
                  death= event(futime, status))
> data1 <- tmerge(data1, subset(nafld3, event=="nafld"), id,
                  nafld = tdc(days))
> data1 <- tmerge(data1, subset(nafld3, event=="diabetes"), id,
                  diab= tdc(days), e1= event(days))
> data1 <- tmerge(data1, subset(nafld3, event=="htn"), id,
                  htn= tdc(days), e2= event(days))
> data1 <- tmerge(data1, subset(nafld3, event=="dyslipidemia"), id,
                  dyslip = tdc(days), e3= event(days))
> attr(data1, 'tcount')
       early late gap within boundary leading trailing tied
death      0    0   0      0        0       0    17549    0
nafld      0   13   0    318        0    3533        0    0
diab    2393    0   0   1058        0       1        0    0
e1      2393    0   0      0     1058       1        0    0
htn     5022    0   0   2045       24       1        5    0
e2      5022    0   0      0     2069       1        5    0
dyslip  8663    0   0   1713       82       2        2    0
e3      8663    0   0      0     1795       2        2    0
```

Four row subject

```
> rowcount <- table(data1$id)
> table(rowcount)    # pick someone with 4 rows
rowcount
    1     2     3     4     5
13501  3122   776   140    10
> subset(data1, id == 135, c(id, age, tstart, tstop, nafld,
                             htn, diab, dyslip, death))
     id age tstart tstop nafld htn diab dyslip death
159 135  40      0   355     1   0    0      0     0
160 135  40    355  2133     1   0    0      1     0
161 135  40   2133  3220     1   1    0      1     0
162 135  40   3220  5269     1   1    1      1     0
```

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The tmerge function

- The first call creates a time window for each subject.
  - For subject 135, this is (0, 5269), ending with censored
  - More complex time windows are supported.
- Each subsequent call, and each term within a call, sequentially adds things into this window
  - tdc: create a time dependent covariate
  - cumtdc: a cumulative time dependent covariate
  - event: create an event covariate
  - cumevent: cumulative event covariate

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```
     id days         event
252 135    0         nafld
253 135  355 dyslipidemia
254 135 2133           htn
255 135 2343  sleep apnea
256 135 3220     diabetes
```

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```
> test <- tmerge(nafld1[, 1:2], nafld1, id,
                 death = event(futime, status))
> attr(test, "tcount")
      early late gap within boundary leading trailing tied
death     0    0   0      0        0       0    17549    0
> #
> subset(test, id==135)
     id age tstart tstop death
135 135  40      0  5269     0
```

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```
> test <- tmerge(nafld1[, 1:2], nafld1, id,
                 death = event(futime, status))
> test <- tmerge(test, subset(nafld3, event=="nafld"), id,
                 nafld = tdc(days))
>
> attr(test, "tcount")
      early late gap within boundary leading trailing tied
death     0    0   0      0        0       0    17549    0
nafld     0   13   0    318        0    3533        0    0
> #
> subset(test, id==135)
     id age tstart tstop death nafld
138 135  40      0  5269     0     1
```

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```
> test <- tmerge(nafld1[, 1:2], nafld1, id,
                 death = event(futime, status))
> test <- tmerge(test, subset(nafld3, event=="nafld"), id,
                 nafl = tdc(days))
> test <- tmerge(test, subset(nafld3, event=="diabetes"), id,
                  diab= tdc(days), e1= event(days))
> attr(test, "tcount")
      early late gap within boundary leading trailing tied
death     0    0   0      0        0       0    17549    0
nafl      0   13   0    318        0    3533        0    0
diab   2393    0   0   1058        0       1        0    0
e1     2393    0   0      0     1058       1        0    0
> #
> subset(test, id==135)
     id age tstart tstop death nafl diab e1
142 135  40      0  3220     0    1    0  1
143 135  40   3220  5269     0    1    1  0
```

```
> test <- tmerge(test, subset(nafld3, event=="htn"), id,
                 htn= tdc(days))
> attr(test, "tcount")
      early late gap within boundary leading trailing tied
death     0    0   0      0        0       0    17549    0
nafl      0   13   0    318        0    3533        0    0
diab   2393    0   0   1058        0       1        0    0
e1     2393    0   0      0     1058       1        0    0
htn    5022    0   0   2045       24       1        5    0
> #
> subset(test, id==135)
     id age tstart tstop death nafl diab e1 htn
155 135  40      0  2133     0    1    0  0   0
156 135  40   2133  3220     0    1    0  1   1
157 135  40   3220  5269     0    1    1  0   1
```

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```
> test <- tmerge(test, subset(nafld3, event=="dyslipidemia"), id
                 lip= tdc(days), e3= event(days))
> attr(test, "tcount")
      early late gap within boundary leading trailing tied
death     0    0   0      0        0       0    17549    0
nafl      0   13   0    318        0    3533        0    0
diab   2393    0   0   1058        0       1        0    0
e1     2393    0   0      0     1058       1        0    0
htn    5022    0   0   2045       24       1        5    0
lip    8663    0   0   1713       82       2        2    0
e3     8663    0   0      0     1795       2        2    0
> #
> subset(test, id==135)
     id age tstart tstop death nafl diab e1 htn lip e3
159 135  40      0   355     0    1    0  0   0   0  1
160 135  40    355  2133     0    1    0  0   0   1  0
161 135  40   2133  3220     0    1    0  1   1   1  0
162 135  40   3220  5269     0    1    1  0   1   1  0
```

Data

- Use any software you want to create the data set, the key is correct *data*.
- Internal rules for `tmerge`
  - If a covariate changes at time t, its new value only affects events that happen after time t, not at or before t.
  - Sometimes we need to delay a covariate (multi-day visits, diltiazem study).
  - Events happen at the end of intervals, covariates change at the beginning.
  - What should happen for data outside the observation range?
    - changes before an interval change the covariate in the interval, but do not extend the range of an interval
    - events outside an observation interval are ignored

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In any sufficiently large sample, any outrageous thing is likely to happen. P. Diaconis and Mosteller, Method of studying coincidences, JASA 1989.

- Someone *will* die on the same day as their diabetes diagnosis, have first NAFLD and first hypertension on the same day, or any number of other overlaps.
- Be prepared to think through these cases.

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Last additions

- age1, age2: age at start and end of interval
- `cstate`: number of metabolic conditions so far
- `endpoint`: censor, 1mc, 2mc, 3mc, death

	endpoint				
cstate	censored	1mc	2mc	3mc	death
0mc	5755	1829	70	4	263
1mc	4650	0	1843	28	243
2mc	3784	0	0	1048	417
3mc	2308	0	0	0	441

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- Why so much time on the data?
- Print out and READ selected subjects from the final result
- If the data set is right, all that follows is easy
- If it is wrong, the answers sometimes don't show it

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Time scale

- Time since diagnosis
  - makes some sense for the NAFLD cases
  - Time since "your number was chosen out of a hat" for the controls?
  - Age and sex need to be in the model, and the model for them nees to be *correct*
  - The population death rate ranges from .03–500 /1000 over this age span; a small lack of fit in the age*sex modeling can dominate all other covariates.
- Age as a time scale:
  - Compares like with like. We can also stratify on sex if desired.
  - Age is not a covariate
- Time since index + case-control matching compares each subject to others of the same age and sex.

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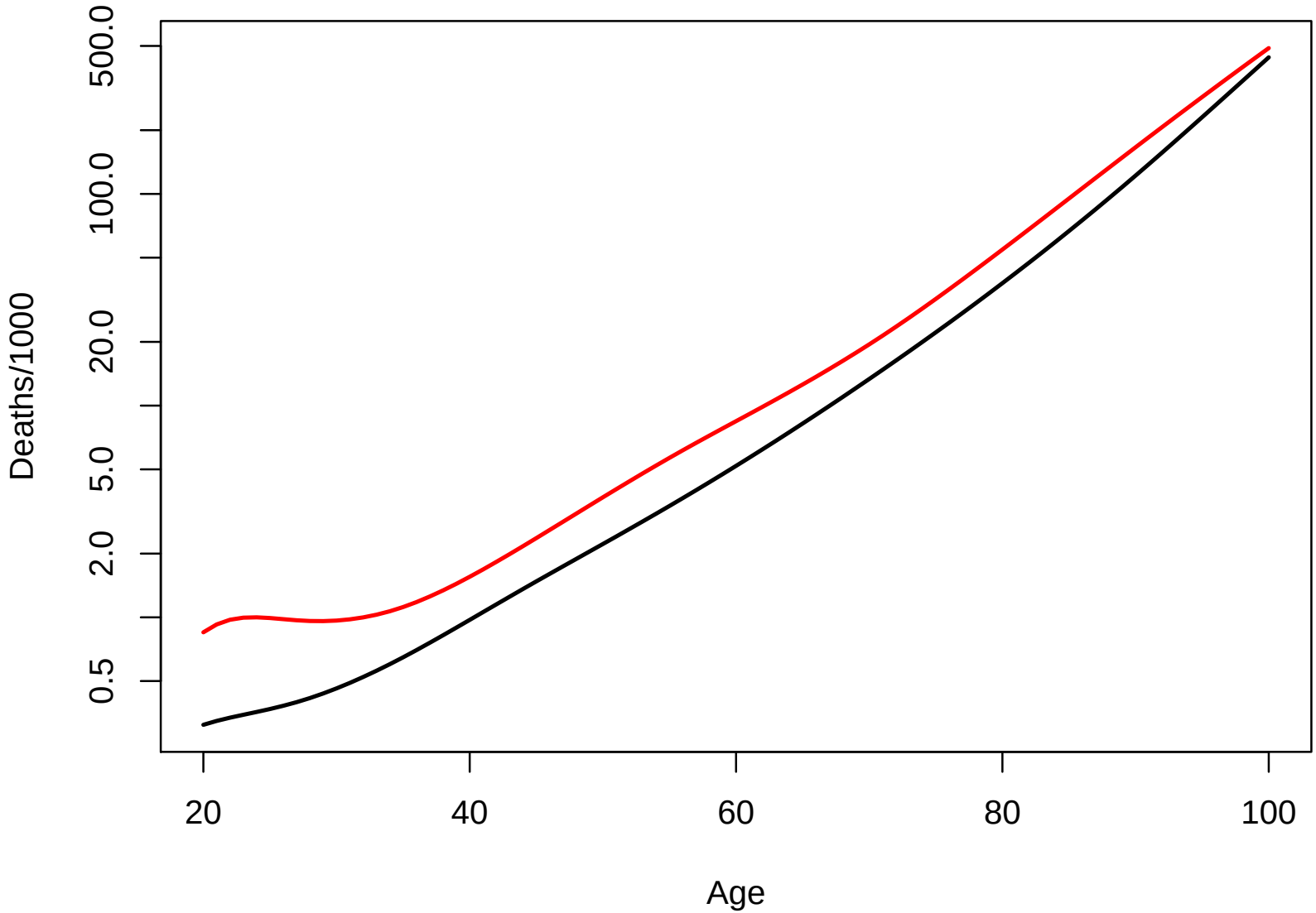
2011 Minnesota death rates



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Fits

```
> nfit1 <- coxph(Surv(age1, age2, death) ~ male + nafld,
                 data=data1)
> nfit2 <- coxph(Surv(age1, age2, death) ~ male + nafld +
                    as.numeric(cstate),
                 data=data1)
> nfit3 <- coxph(Surv(age1, age2, death) ~ male +
                   strata(cstate)/nafld,  data= data1)
> nfit4a <- coxph(Surv(age1, age2, endpoint %in% c("1mc", "2mc",
                       strata(male) + nafld,
                 data=data1, subset= (cstate=="0mc"))
> nfit4b <- coxph(Surv(age1, age2, endpoint %in% c("2mc", "3mc")
                      strata(male) + nafld,
                 data=data1, subset= (cstate== "1mc"))
> nfit4c <- coxph(Surv(age1, age2, endpoint=="3mc") ~
                      strata(male) + nafld,
                 data=data1, subset= (cstate=="2mc"))
```

	male sex	NAFLD	mcount
Alive -> Dead	1.4	1.6	
Alive -> Dead	1.4	1.5	1.2
0 MC -> Dead	1.4	1.9	
1 MC -> Dead	1.4	1.7	
2 MC -> Dead	1.4	1.7	
3 MC -> Dead	1.4	1.1	
0 MC -> 1+ MC	2.5	2.5	
1 MC -> 2+ MC	1.7	1.7	
2 MC -> 3 MC	1.6	1.6	

- The incremental impact of NAFLD on death decreases
- The impact on conversion to the next comorbid state decreases.
- (Allen adds these to figure 4.)

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Stacked data set

Build a transtion matrix.

```
        to
from     0mc 1mc 2mc 3mc death
  0mc      -   1   2   3     7
  1mc      -   -   4   5     8
  2mc      -   -   -   6     9
  3mc      -   -   -   -    10
  death    -   -   -   -     -
```

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```
> # data creation suppressed
> dim(msdata)
[1] 65223    23
> msdata[1:5, 1:7]
An object of class 'msdata'

Data:
  from to trans status id age male
1    1  2     1      0  1  57    0
2    1  2     1      0  2  67    0
3    1  2     1      0  3  53    1
5    1  2     1      1  5  68    1
7    1  2     1      0  6  39    0
```

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	to						
from	0mc	1mc	2mc	3mc	death	no event	total entering
0mc	0	1829	70	4	263	5755	7921
1mc	0	0	1843	28	243	4650	6764
2mc	0	0	0	1048	417	3784	5249
3mc	0	0	0	0	441	2308	2749
death	0	0	0	0	0	1364	1364

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All at once

```
> msdata$sgrp <- factor(with(msdata, from + 4*(to==5)))
> allfit2 <- coxph(Surv(age1, age2, status) ~
                        sgrp:(nafld + male) + strata(from, to
                   data=msdata)
> length(coef(allfit2))
[1] 14
```

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Other summaries

- Hazard rates between states
- $p(t)$, state vector at time t
- Mean time in state
- Number of visits to each state

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Aalen-Johansen

```
> multi <- survfit(Surv(age1, age2, endpoint) ~ nafld, data
                   istate=cstate, id=id, se=FALSE, start.time

Error in survfitCI(X, newY, weights = casewt, id =
id, istate = istate, :  subject is in two different
groups, id 13
```

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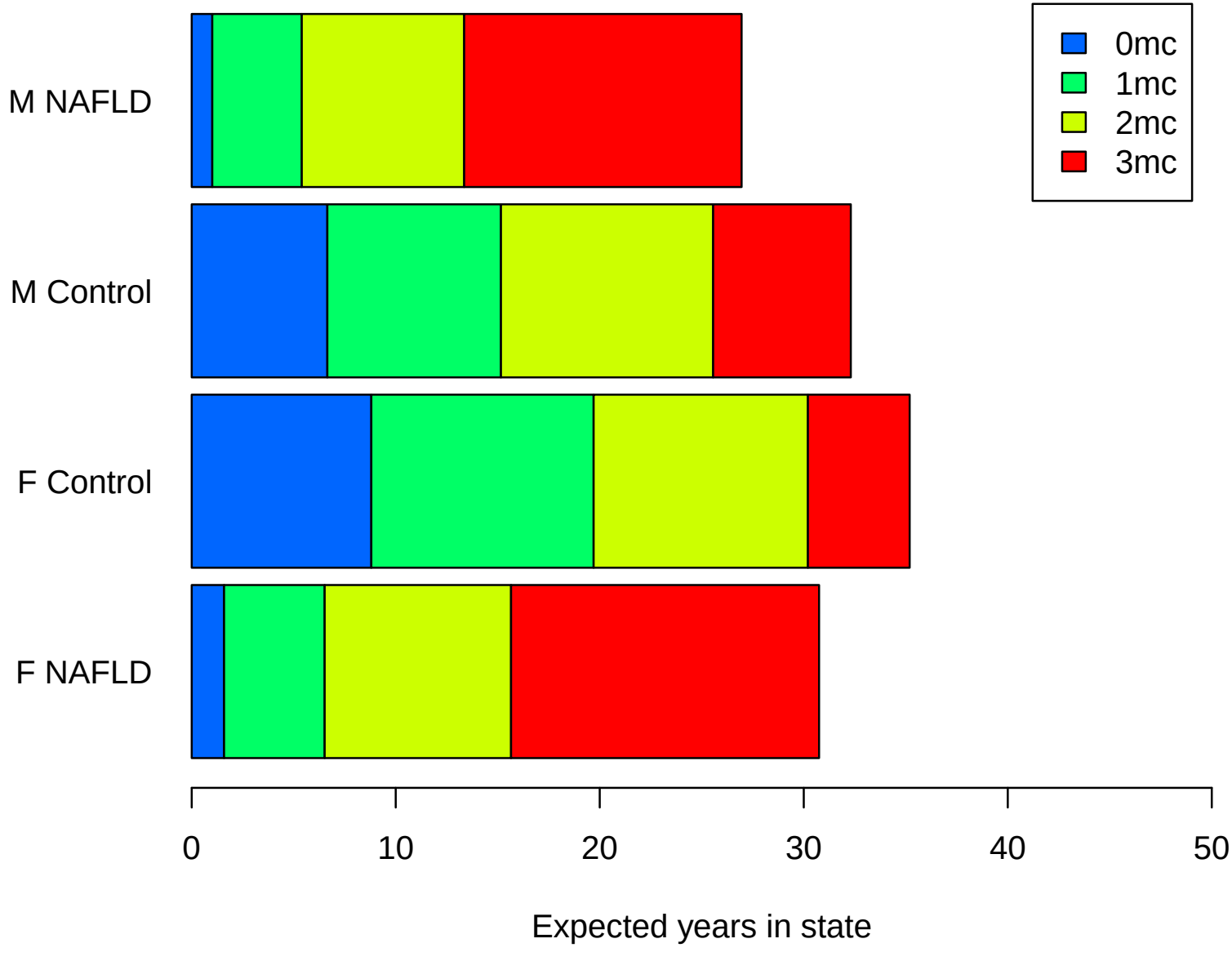
```
> data1$nbase <- data1$nafld[match(data1$id, data1$id)]
> multi1 <- survfit(Surv(age1, age2, endpoint) ~ male+ nbas
                    istate=cstate, id=id, se=FALSE, start.time
> print(multi1, digits=2, rmean=100)
Call: survfit(formula = Surv(age1, age2, endpoint) ~ male +
    data = data1, id = id, istate = cstate, se = FALSE, sta

                              n nevent rmean*
male=0, nbase=0, 1mc   7188    556   10.9
male=0, nbase=1, 1mc   1791     74    4.9
male=1, nbase=0, 1mc   5935    424    8.5
male=1, nbase=1, 1mc   1492     55    4.4
male=0, nbase=0, 2mc   7188    596   10.5
male=0, nbase=1, 2mc   1791    176    9.1
male=1, nbase=0, 2mc   5935    547   10.4
male=1, nbase=1, 2mc   1492    151    8.0
male=0, nbase=0, 3mc   7188    290    5.0
male=0, nbase=1, 3mc   1791    164   15.1
male=1, nbase=0, 3mc   5935    285    6.7
```


M NAFLD
M Control
F Control
F NAFLD
0mc
1mc
2mc
3mc
0
10
20
30
40
50
Expected years in state

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	0mc	1mc	2mc	3mc	death
male=0, nbase=0	0.54	0.33	0.09	0.03	0
male=0, nbase=1	0.20	0.31	0.27	0.21	0
male=1, nbase=0	0.48	0.36	0.12	0.04	0
male=1, nbase=1	0.13	0.37	0.27	0.22	0

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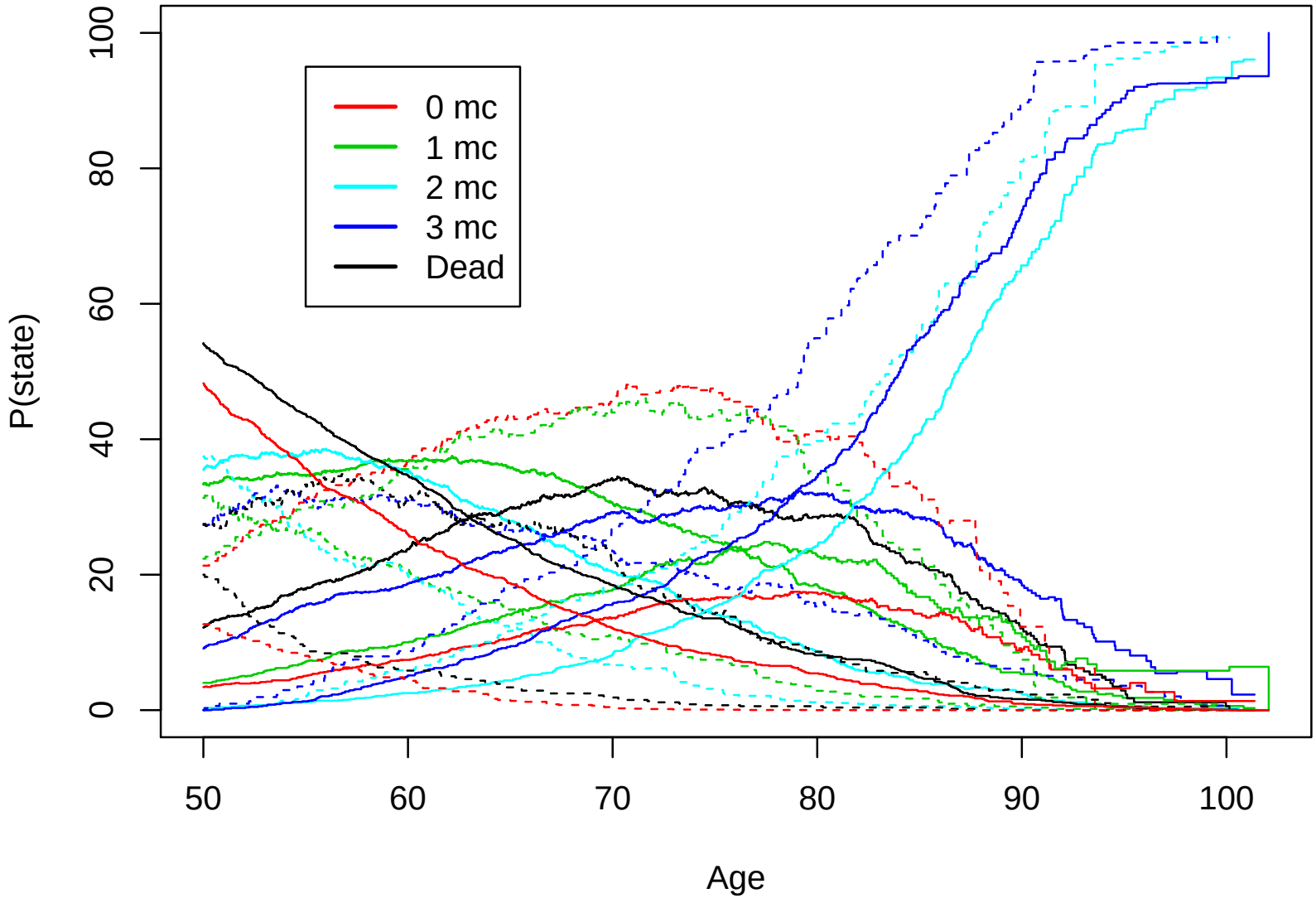
0 mc
1 mc
2 mc
3 mc
Dead
P(state)
0
20
40
60
80
100
50
60
70
80
90
100
Age

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Fool survfit

```
> fakeid <- data1$id + data1$nafld/2
> multi2 <- survfit(Surv(age1, age2, endpoint) ~ nafld, dat
                    istate=cstate, id=fakeid, se=FALSE, start.
> print(multi2, digits=2)
Call: survfit(formula = Surv(age1, age2, endpoint) ~ nafld,
    id = fakeid, istate = cstate, se = FALSE, start.time =

                      n nevent rmean*
nafld=0, 1mc    13036    972    9.9
nafld=1, 1mc     3617    137    4.8
nafld=0, 2mc    13036   1120   10.6
nafld=1, 2mc     3617    350    8.6
nafld=0, 3mc    13036    550    5.7
nafld=1, 3mc     3617    328   14.3
nafld=0, death 13036    931   18.0
nafld=1, death  3617    369   23.0
nafld=0, 0mc    13036      0    7.8
nafld=1, 0mc     3617      0    1.3
```

- This fit allows someone to jump to another curve mid-stream.
- For simple alive-dead, these curves are equivalent to Simon and Makuch, Statistics in Medicine, 1984.

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Choices

1. Use only baseline values for the fit
   - Survival given that baseline
   - Subjects will evolve, and that gets built into the coefficients and the baseline hazard
   - The PH assumption may be badly strained
2. "Baseline" values at future times (landmark analysis)
3. Use time-dependent covariates for the fit
   - 3.1 Predict for fixed covariates
   - 3.2 Create a fixed covariate path (delicate)
   - 3.3 Joint fits (JM package)
   - 3.4 Use a population average
   - 3.5 Encode the path as states and refit
4. Various bad ideas

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Time in state, based on a fitted model

- Simplest method is 3.1: time-dependent fit + prediction for static covariates
  1. Fit the TD models for each state to state transition (`nfit3`, `nfit4a`, `nfit4b`, `nfit4c`)
  2. For each model, get the predicted hazard functions $\lambda_{ij}(t,$ control) and $\lambda_{ij}(t,$ NAFLD)
  3. Compute Aalen-Johansen estimates using these values.
  4. Alternate: use the `mstate` package
- Better is method 1: time-fixed covariate fit + static prediction
  1. Only use the baseline nafld value, or create the doubled data set (full follow-up for controls that become cases)
  2. Cox model fits for each transition, robust variance if doubled
  3. Hazard estimates and AJ computation as before
- Better is method 3.3: time-dependent fit + population curves
  1. Fit the TD models
  2. Predicted hazard curves for *each covariate path* = 334 for controls, only 1 for NAFLD; overall hazard for controls is a time-weighted average.
  3. Use these to compute Aalen-Johansen values

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Predicting the future

- When there are time-dependent covariates, how do you predict future outcomes?
- What do you want to predict?
  - Outcome risk given baseline covariates, covariates do not change?
  - Outcome risk given covariates, covariates evolve?

MAYO CLINIC

Predicting the future

- When there are time-dependent covariates, how do you predict future outcomes?
- What do you want to predict?
  - Outcome risk given baseline covariates, covariates do not change?
  - Outcome risk given covariates, covariates evolve?
- Current smoker:
  - risk of MI for this subject, if they continue smoking
  - risk for a population of current smokers, knowing some will quit
- What about systolic blood pressure?

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Primary biliary cirrhosis

- Progressive autoimmune disease
- Continual inflammation slowly creates scar tissue
- Time dependent risk score fits better

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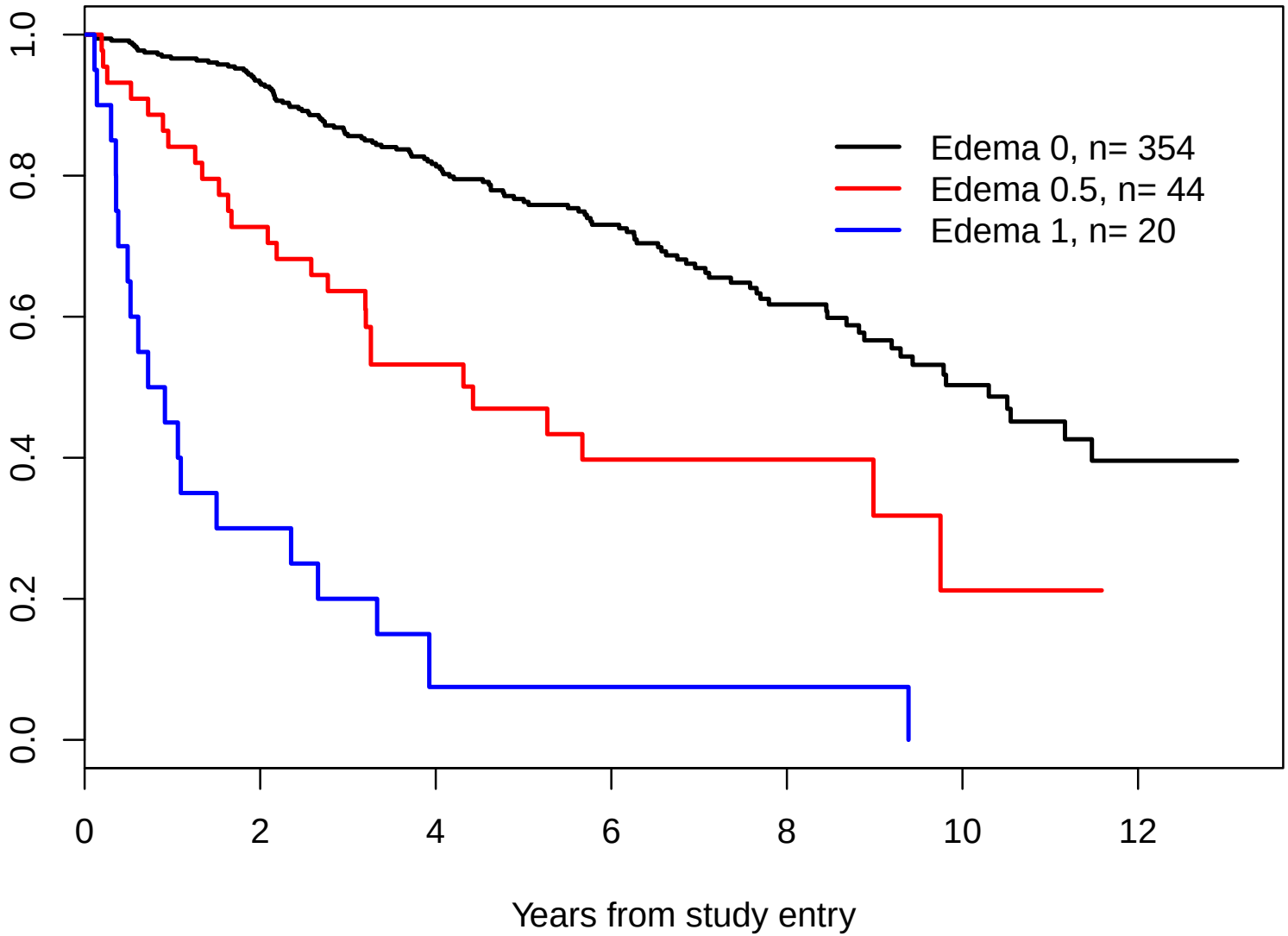
Primary biliary cirrhosis



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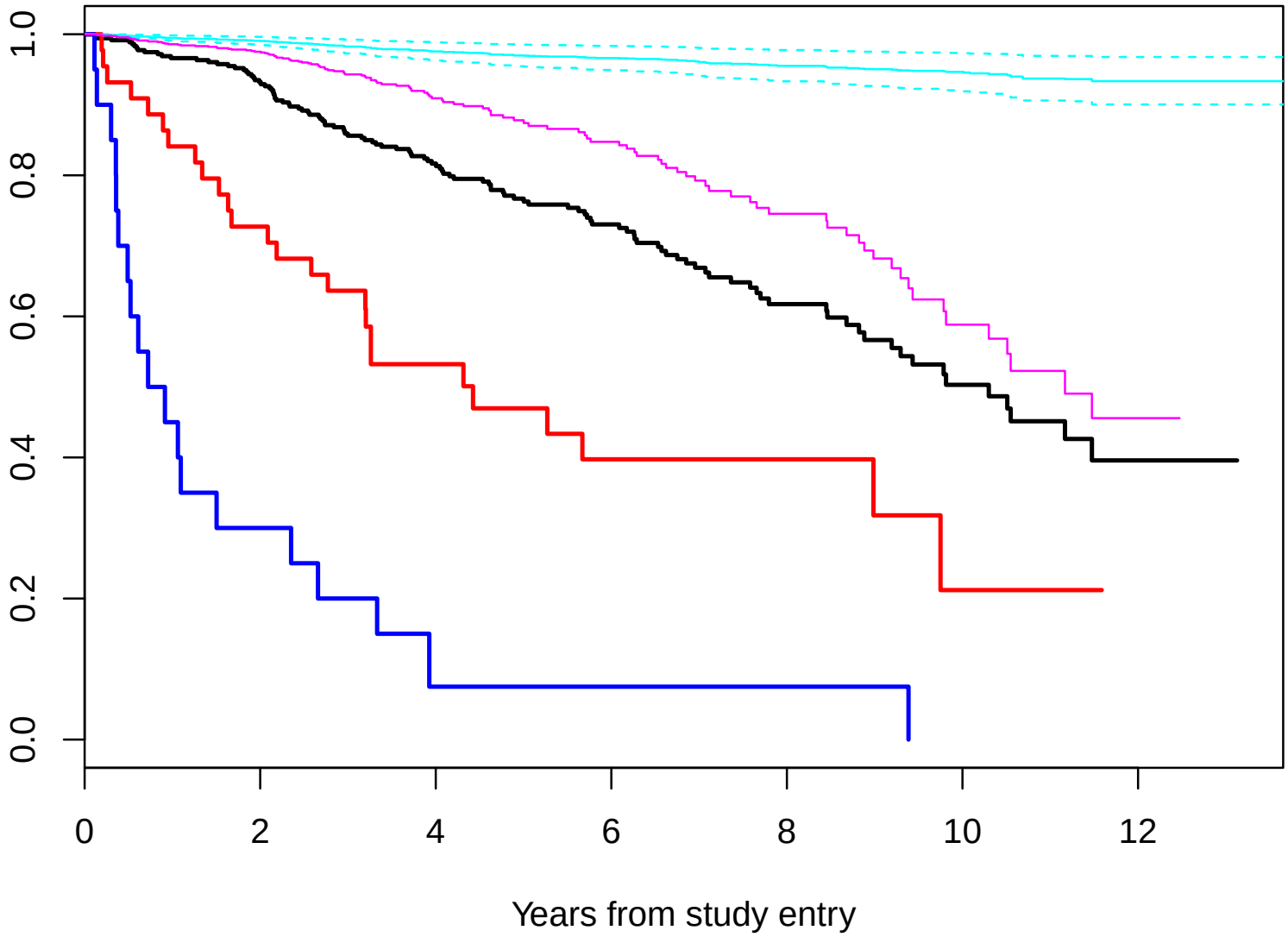

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Using mstate

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Population averages

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Issue

- Natural summaries
  - transition rate λ_{jk} from state j to state k
  - $p(t)$, the probability-in-state vector
  - $E_j(t)$, expected amount of time in state j
  - $v_j(t)$, expected number of visits to state j (lifetime risk)
- Hazard models for λ are natural
- Coefficients from the hazard models do not translate in a simple way to the other summaries.

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Fundamental Issue

We are infatuated with simplicity.

$$\log(\lambda(t)) = \beta_0(t) + \beta_1 x_1 + \beta_2 x_2 + \ldots$$

- This is the proportional hazards model
  - The only time-varying coefficient is β_0, the "baseline hazard"
  - All terms are linear, no interactions
- If it holds, then the effect of any given covariate is captured by the one number summary $\exp(\beta)$ = hazard ratio.
- What is remarkable is how well this model fits the data for acute endpoints such as time to death for subjects with advanced cancer, or waiting time on an organ transplant list.
- The model can be stretched to cover repeated events of the same type, but not always.

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Why focus on simplicity

- Terse summaries for our papers
- Too many projects on our plate
- Thoughtful simplicity: models which over-summarize are fit in order to better understand the data, but with the larger context always in mind.

MAYO CLINIC

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"All models are wrong, the question is whether they are wrong enough to not be useful." GEP Box
"A model is a lie that helps you see the truth." Howard Skipper

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"A model is a lie that helps you see the truth." Howard Skipper
"For every complex question there is a simple and wrong solution." A Einstien

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Marginal estimates

- model with x_1, x_2, x_3, ...
- $PMM_{x1=c} = E_X(\hat{y}(x)|x_1 = c)$
- Population Marginal Mean
- Idea
  - Compare treatment A to treatment B
  - Pretend we have a population of subjects = the other covariates
  - For each of those subjects we can compute the predicted response for their covariates, under treatment A and then under treatment B
  - Take an average; $PMM_A - PMM_B$

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Implement

- Which $\hat{y}$
- What population for the other covariates X
  - data set as a whole
  - fixed data set, e.g., US 2000 age/sex distribution
  - external data set (calibration)
  - balanced factorial design (Yates, 1934)
- Computation.
  - simple approach: brute force
  - `yates` function
- Standard error
  - simple in a few cases
  - parametric simulation
  - other?
  - open issue

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Old idea

- $\hat{y} = S(t)$, population=data: direct adjusted survival
- linear model, $\hat{y} = X\hat{\beta}$, population=data: closely related to survey sampling estimates
- g-estimates of causal modeling — sort of
- first instinct of a statistician is to change Z to $E(Z)$

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- first instinct of a statistician is to change Z to $E(Z)$
- linear model, $\hat{y} = X\hat{\beta}$, population= factorial for the categoricals, data for continuous: SAS GLM type III (SGTT)
  1. clever and efficient formulas, but forgot what is being computed
  2. horrible documentation (document an algorithm)
  3. factorial population is rarely appropriate
  4. other SAS (and R) procedures do something different (NSTT)

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Issues

- The model has to be correct
- $\hat{y}$ should be unbiased
  - since many values will be averaged, bias is more worrisome than variance
  - model will often be "rich" wrt x_1 shape and/or interactions with other variables
  - similar to the thinking used in propensity scoring
- Convince our clients that not everything is a hazard ratio
  - Expected time in state (RMST)
  - Expected number of visits
- More computation
- Variance and power need exploration

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Mayo Clinic Study of Aging

- On autopsy, Alzheimer's patients have amyloid plaques and neurofibrollary tangles in their brain tissue.
- The population is aging.
- Studies
  - Alzhiemer's Disease Neuroimaging Initiative (ADNI)
  - Religious Orders Study (ROS), Memory and Aging Project (MAP)
  - Mayo Clinic Study of Aging (MCSA)
    - Enroll a stratified population sample
    - Equal number of males and females, larger cohorts at older ages
    - Follow all subjects at a regular intervals
    - Replenish the cohort for drop-out and death.

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Key Measurements

- Clinical assessment
  - Cognitive tests
  - Care team

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- MRI structural scan
- Amyloid PET
- FDG PET
- Tau PET

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Key Measurements

- Clinical assessment
  - Cognitive tests
  - Care team
- MRI structural scan
- Amyloid PET
- FDG PET
- Tau PET
- CSF tau and fractions

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Enrollment

- Ever enrolled 2659 females, 2705 males
- Carrying capacity of 2500–2700
- Clinical visits every 15 months
- Imaged subset: 2794
  - Neurodegeneration: 2763
  - Neurodegeneration and amyloid: 1795
  - Neurodegeneration, amyloid, and tau: 656

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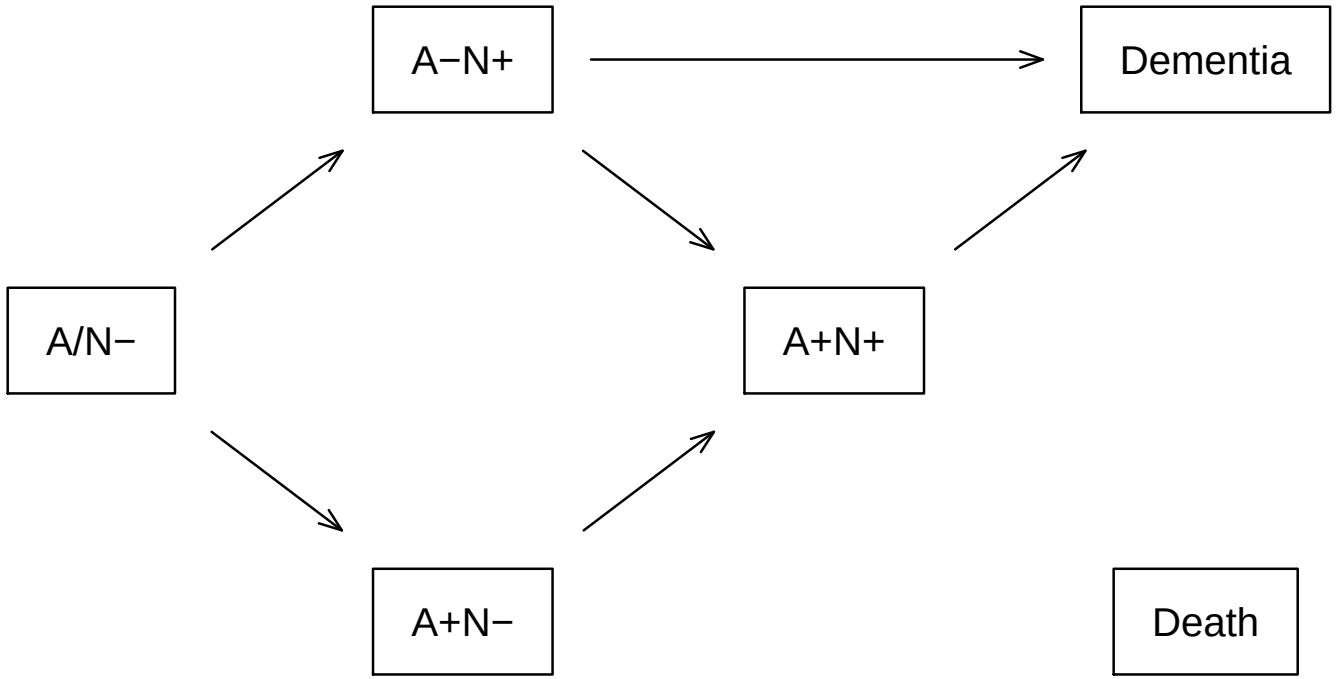
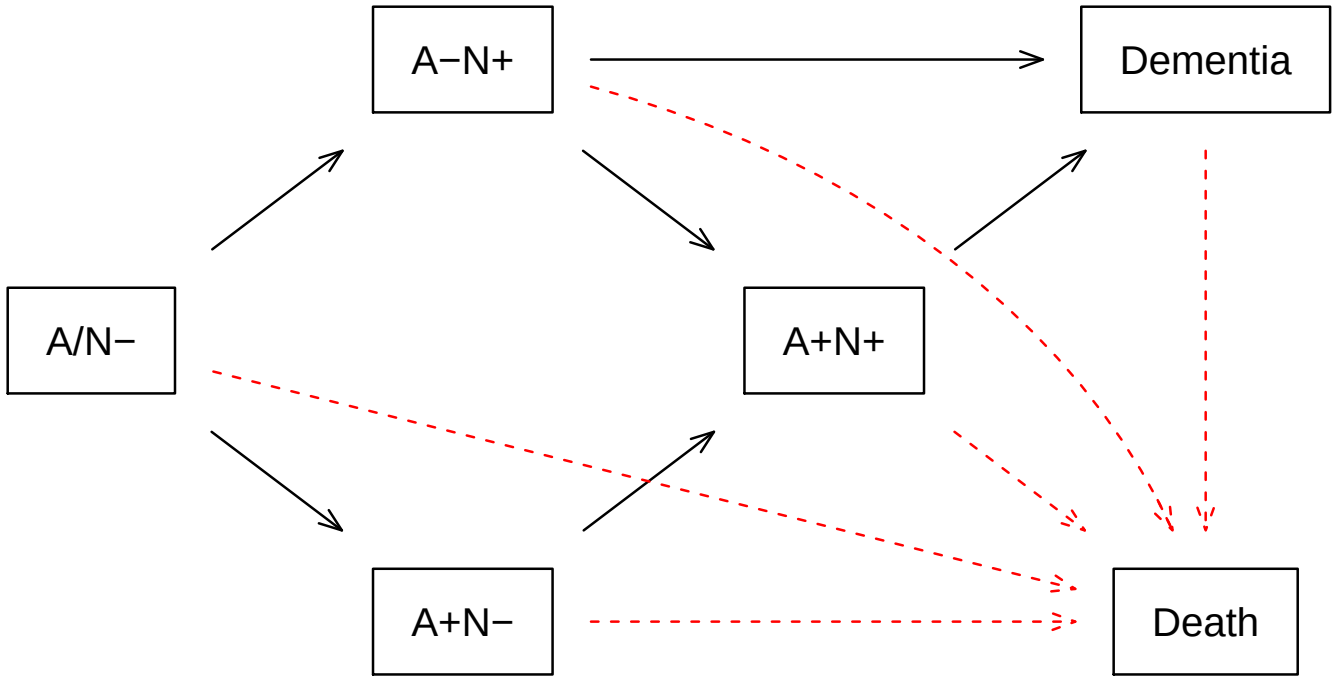

A−N+
Dementia
A/N−
A+N+
A+N−
Death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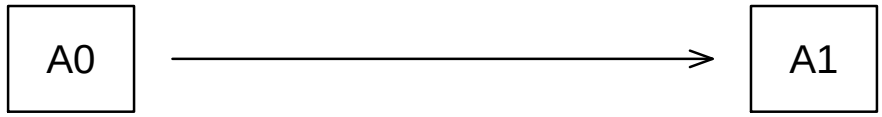

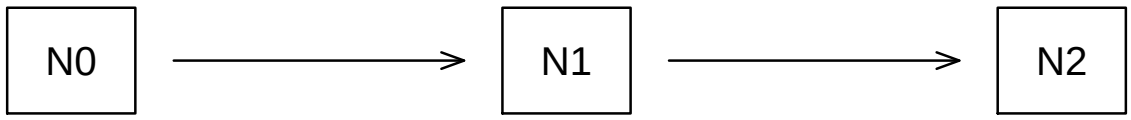

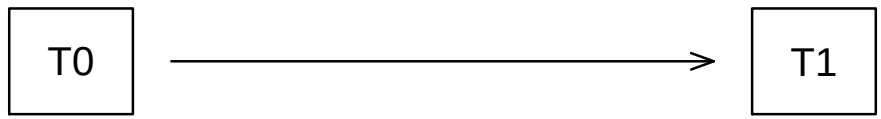

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States

- A0/A1: none/mild vs moderate/severe amyloid burden
- T0/T1: none/mild vs moderate/severe tau burden
- N0/N1/N2: increasing neurodegeneration
- 13 states (boxes)
- 32 transitions (arrows)

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- 5 covariates: intercept, age, sex, APOE positivity, hypertension
- 32 transitions
- 160 potential parameters
- plus HMM parameters

MAYO CLINIC

- 5 covariates: intercept, age, sex, APOE positivity, hypertension
- 32 transitions
- 160 potential parameters
- plus HMM parameters
- Don't get carried away!

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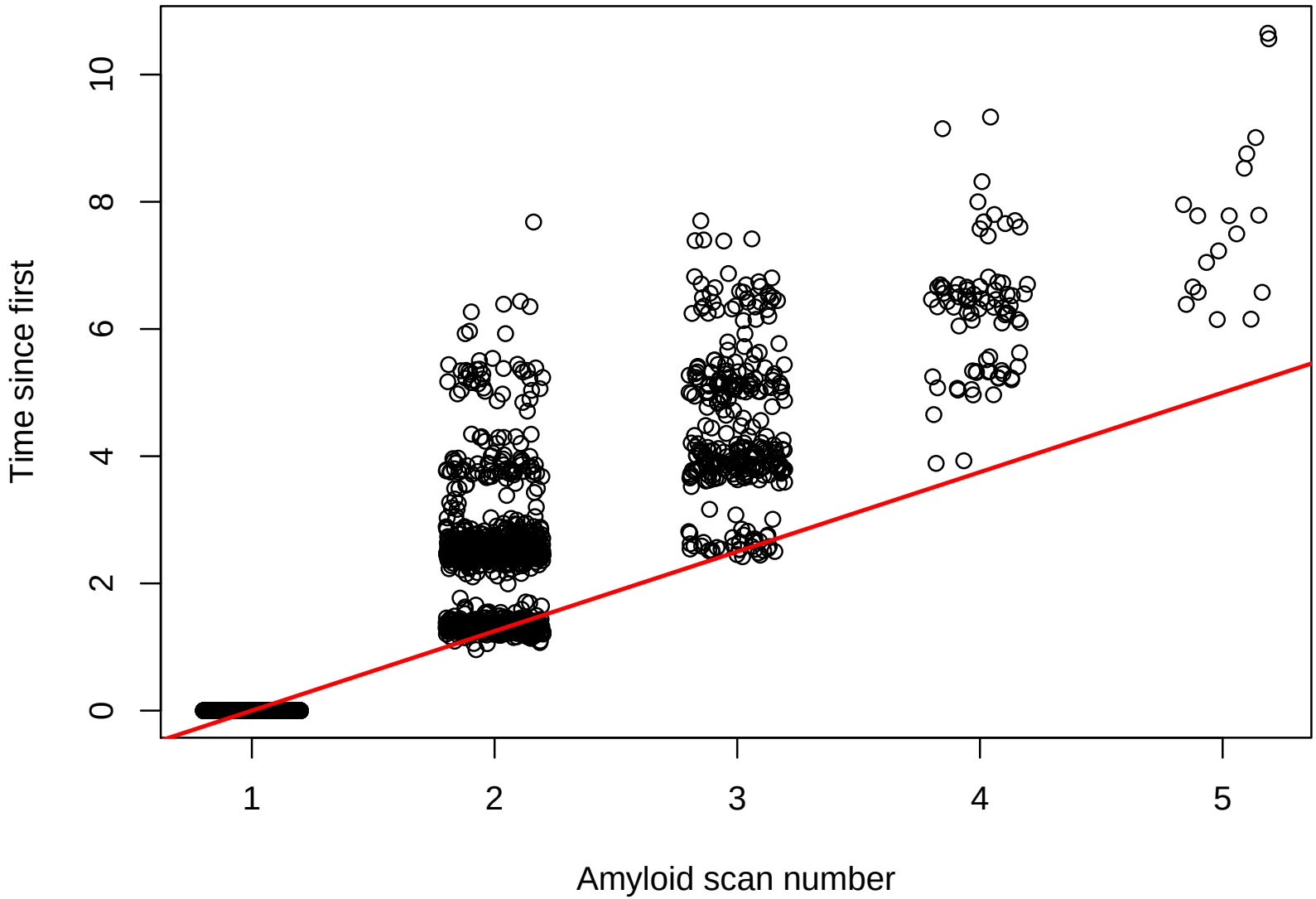
Amyloid scan timing



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Interval censoring

- Standard survival
  - (t, s) time t at which subject entered state s
  - Kaplan-Meier, Cox model, parametric AFT, ...
  - Multi-state is a simple extension
- Panel data
  - (t, s) time t at which the subject was measured, they were in state s at that time
  - Exact same box and arrow diagram
  - Same parameters: $\lambda_{jk}(t)$, time in state, visits, ...
  - Completely different software
  - `msm` in R

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Key assumptions

- Standard survival
  - Delays are small enough that "time till we saw it" is a good surrogate for "time until it happened"
  - Non-informative censoring
- Interval censored
  - Hazard is constant over the intervals between visits (or a smooth model)
  - Non-informative visits

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Hidden Markov Model

- The data consists of time, outcomes and covariates
  - The state is not observed directly, rather we see one or more outcomes that depend on the underlying state.
  - No need for (time1, time2, endpoint) notation
  - Data will have missing values, e.g., covariates on the day of death
- Same box and arrow model for the states, covariates connect to λ as before
- Another set of parameters for the arrows that connect state to outcome
- Allows for more episodic data.
- Much of the software is special purpose.

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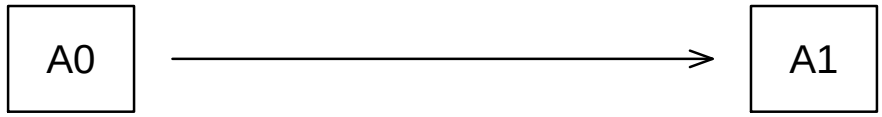

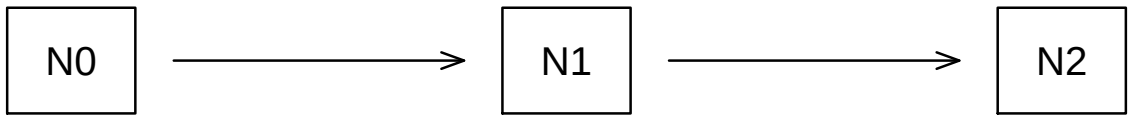

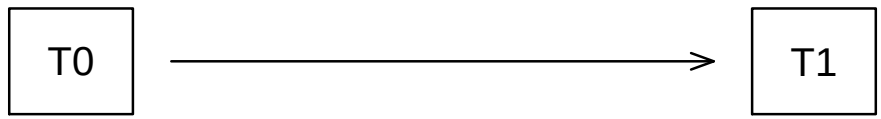

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- log(measured amyloid binding) $\sim N(A^-/A^+, \sigma)$
- global memory score $\sim N(\mu, \tau)$
  $\mu = \beta_0 + \beta_1 N + \beta_2 \text{sex} + \beta_3 \text{education}$
- A^- : A^+ rate depends on APOE status, but on gender
- N transition rates depend on A but not vice-versa

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HMM

- Very powerful concept
- Downsides
  - Easy to get carried away
  - Computation is *much* harder than a Cox model
    - good starting estimates
    - compute cluster
    - patience
  - Few model checking methods
  - Long manual

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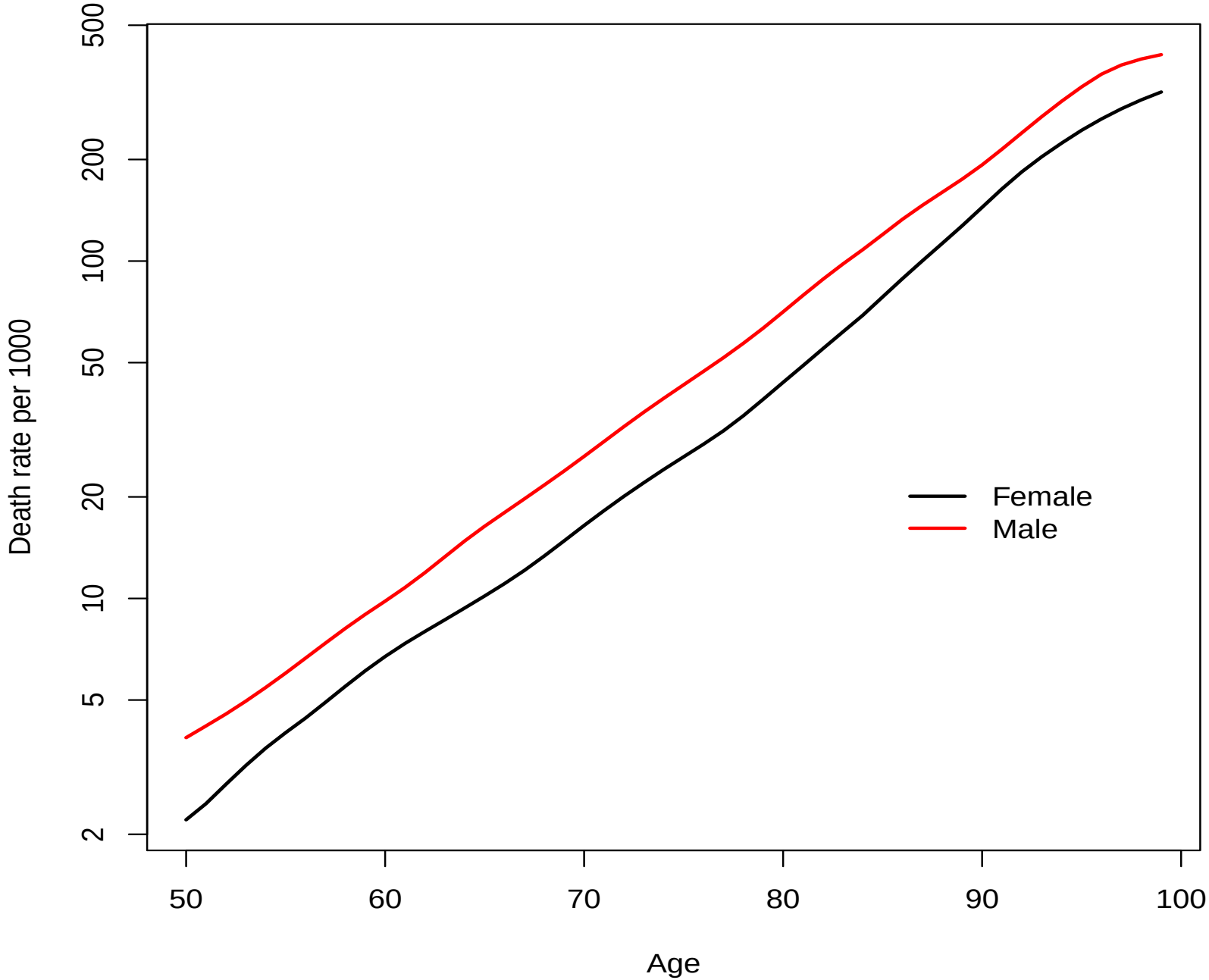
Death rate per 1000
2
5
10
20
50
100
200
500
50
60
70
80
90
100
Age
Female
Male

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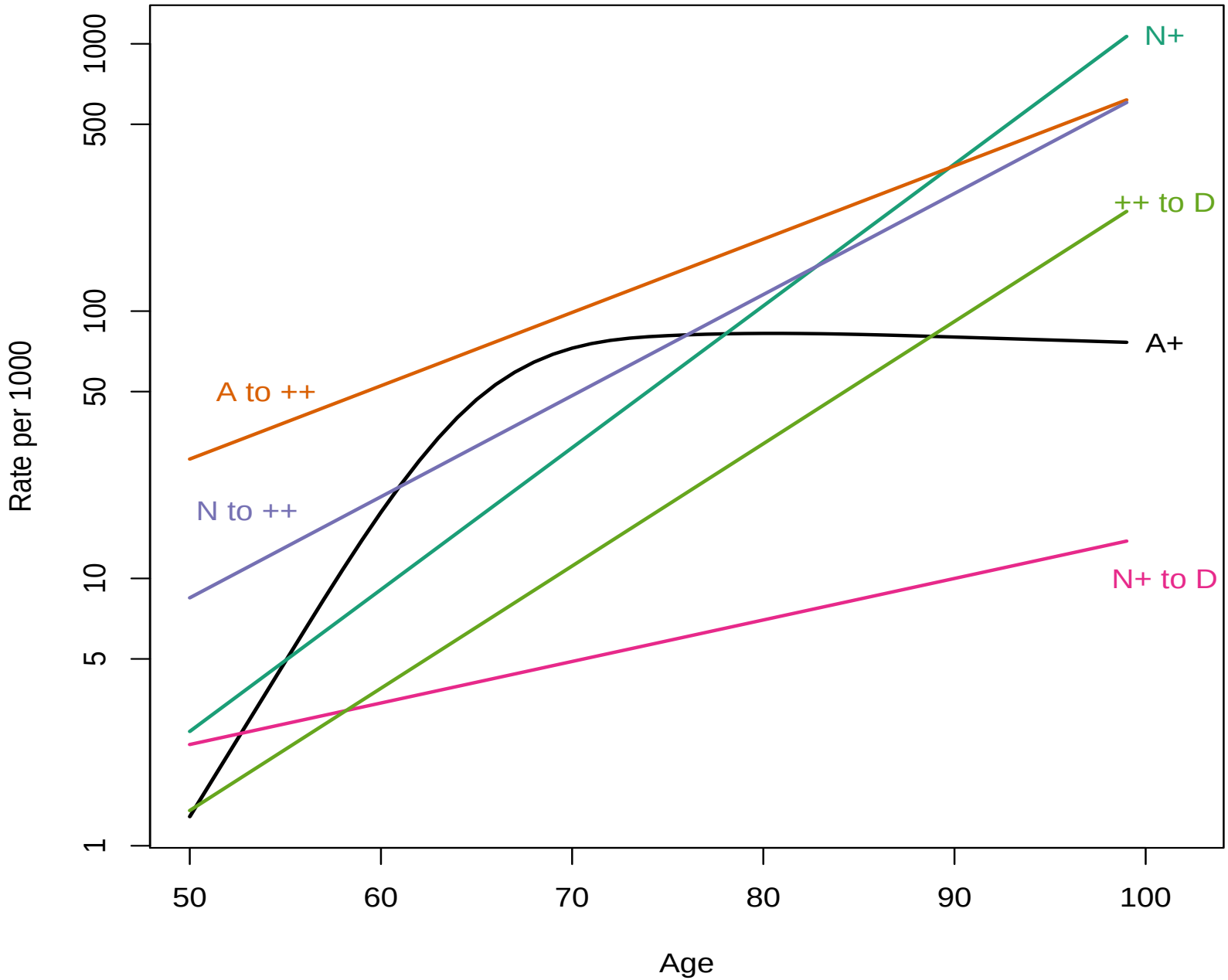
Rate per 1000
1
5
10
50
100
500
1000
50
60
70
80
90
100
Age
N+
++ to D
A+
A to ++
N to ++
N+ to D

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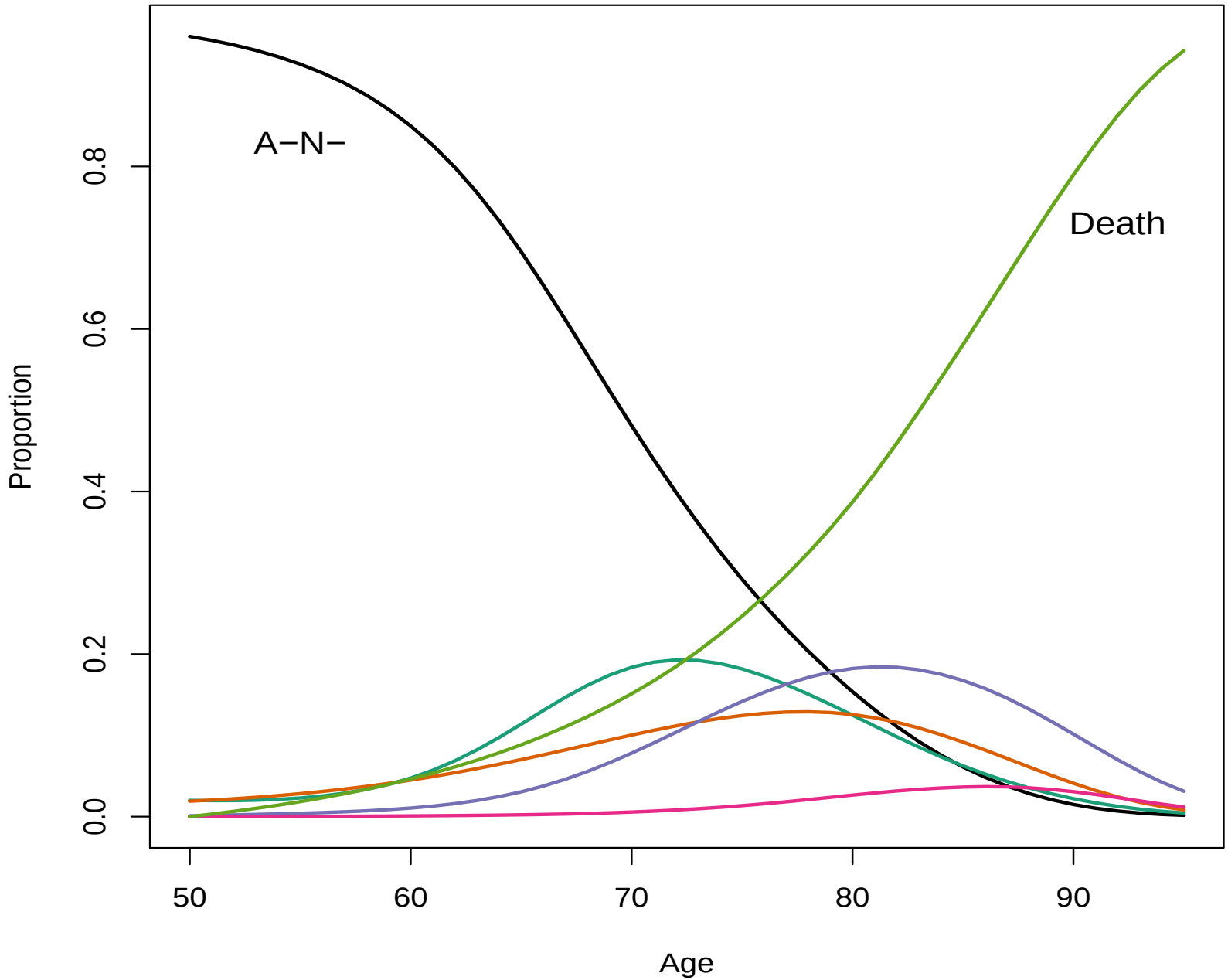

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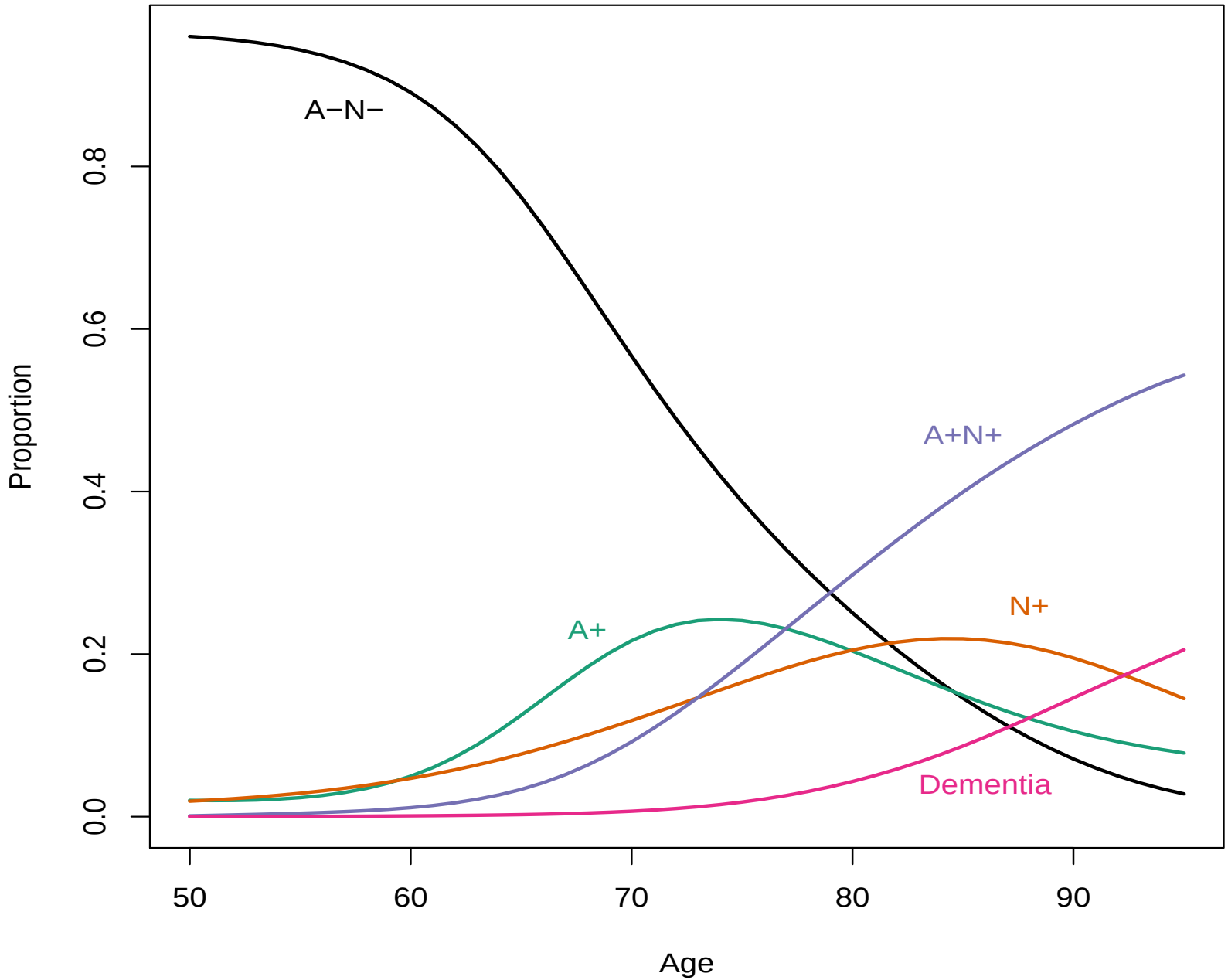

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Results

- Rates
  - What is the pattern of rates?
    - The T0→T1 rate is higher in the presence of A1, but not vice versa. (Amyloid deposits promote tau.)
    - A1/T1 promotes changes in N
  - The role of covariates.
    - A positive APOE genotype affects A0/A1 transitions, but not others.
    - Other covariates affect N but not A or T
- Outcomes
  - What is the probability of ever visiting the N2 state?
  - What is the average duration of time spent in N2?
  - What is the predicted fraction who go down each path?
  - What is the impact of a change in one rate?

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Conclusions

- Multi-state data ranges from the simple to the complex
- Good tools are available
- You need more than just a hazard ratio
- There is wide opportunity for new methods and software

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Model checks and time-dependent covariates

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Model checks

- We tend to assume
  - Linear functional form
  - Additivity
  - Proportional hazards
  - Lack of leverage (outliers)
- $\lambda_i(t) = \lambda_0(t)\exp(\beta_1 x_1 + \beta_2 x_2 + \ldots)$
- Is any of it true?

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  - Linearity fails when X has a wide range. (creatinine)
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Time-dependent covariates

The Cox model likelihood is set up like a lottery.
At each death time:

- Risk set = set of subjects *at risk* for death
  (if they had died, we would have recorded it)
- Score = $r = \exp(X\beta)$ = "number of tickets"
- $L = r_d / \sum r_i$ = Pr(the person who won, should have won)
- Choose β to maximize L

$$C = \frac{\sum_{deaths} \text{number with lower score } r \text{ than the winner}}{\sum_{deaths} numberatrisk}$$

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Advantages

- At each death time you only need to know who is present
  - people can enter and leave
  - delayed entry
- Covariates can be those *relevant for this drawing*
  - most recent lab tests
  - time delays (delayed action of a drug)
  - rate of change

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  - rate of change
- easy coding

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Disadvantages

- Today is all that matters
  - Effects are assumed to be instantaneous

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Disadvantages

- Today is all that matters
  - Effects are assumed to be instantaneous
- Effects are constant (until next measurement)
- Almost too easy to use

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How to do it wrong

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Survival by treatment response

- At the end of a trial a survival curve is made comparing those who *responded* to those who did not.
  - responders have a better curve!
  - the p-value is $< .01$!
  - stop the presses!

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  - stop the presses!
- The result is guaranteed – why?
- The original analysis of the Stanford study
- Rediscovered every 3–5 years

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Simulation

- Advanced lung cancer data set
- Assume bi-monthly visits
- Randomly mark 5% of the subjects "winners" at each visit.

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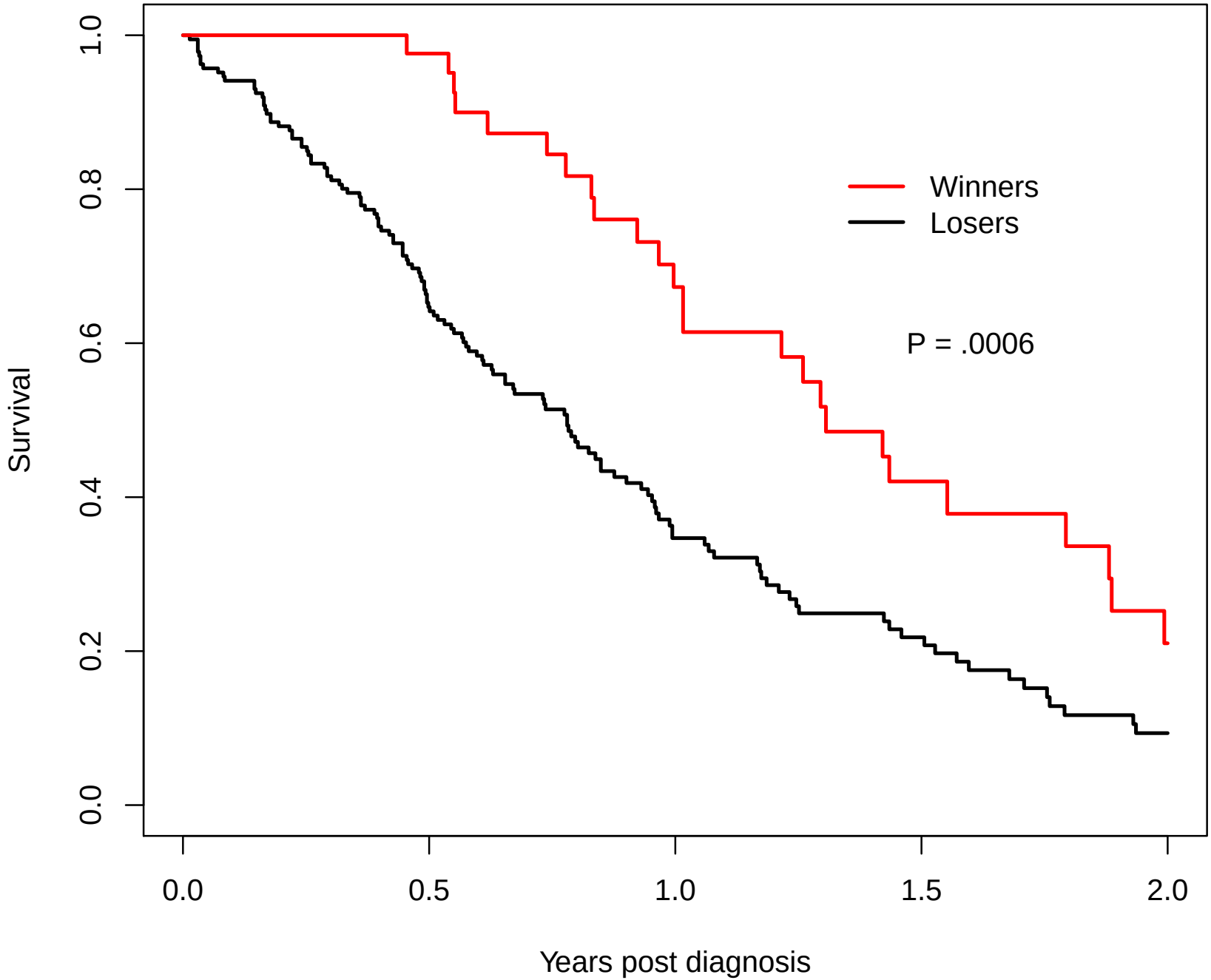
Survival
1.0
0.8
0.6
0.4
0.2
0.0
Winners
Losers
P = .0006
0.0
0.5
1.0
1.5
2.0
Years post diagnosis

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The surprise is how *big* the error can be.

- Stanford Heart, time dependent transplant: .99 (.54, 1.8)
- Stanford Heart, ever transplant: .17 (.10, .28)
- Gail, "Does cardiac transplantation prolong life? A reassessment." Ann Int Med 1982.

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Cumulative dose received

- Does dose reduction harm patients?
- x= cumulative dose received

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Cumulative dose received

- Does dose reduction harm patients?
- x= cumulative dose received
- x= fraction of expected

MAYO CLINIC

Cumulative dose received

- Does dose reduction harm patients?
- x= cumulative dose received
- x= fraction of expected
- x= fraction of expected, to date
- Redmond, Cancer Treatment Reports

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Prophetic variables

Some time-dependent covariates are not predictors of an event as much as they are markers of a failure-in-progress:

- Medication changes
  - Cessation of diuretics in heart failure
- Multiple-organ failure
- Ventilation

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- Medication changes
  - Cessation of diuretics in heart failure
- Multiple-organ failure
- Ventilation
- "Have called the priest"
- Tautologies: lab test Tuesday, progression Wed
- Consider time delays

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Errors

- Placebo controlled trial
- Adverse reaction to active arm (rare, but expected)
- "Weeks on drug" add to the form

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```
data new; set old;
    futime = fu_date - entry_dt;
    tstart =0;
    if (drug_weeks ne . and drug_weeks < futime/7) then do;
       * one of the crossover patients;
       tstop = drug_weeks *7; event = 0;   output;
       tstart= tstop; tstop=futime;
       arm =0; event = status; output;  *cross to placebo;
       end;
    else do; * no crossover;
      tstop=futime; event=status; output;
      end;

proc phreg (tstart, tstop) * status(0) = arm;
```

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Time delay

- Delayed labs
- UDCA
- Long term prediction
- Option in the `tmerge` function.

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Immortal time bias

Subjects are treated as 'at risk' when they actually are not.

- At risk: If the subject had had an event, we would have seen and recorded it.

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- At risk: If the subject had had an event, we would have seen and recorded it.
- rhDNase study
- Time gaps in the REP
- Oscar winners live longer
- ever prescribed inhaled corticosteroids = asthmatic
- "at least 2 instances", then use the first one

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More

- Mark an adverse event as midway between visits
- Delete subjects who do not complete treatment
- Interpolate a lab value
- Add "average death rate" as a covariate
- Multi-state models create new opportunities for error
- ...

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- ...
- Process
  - Think through special cases
  - Create the (start, stop] data set
  - Print out a portion and *read* it.
  - Think, pause, think
  - If results are too good to be true ...

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Summary

Time dependent covariates are a wonderful tool.

1. You must not look into the future.

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4. Duration or rate variables work surprisingly rarely.
5. Bad things happen if you look into the future.
6. Short term prediction is uninteresting.
7. It is challenging to draw survival curves.

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Survival curves

- By definition, a survival curve is a look into tomorrow, given *what you know today*.
- In a time dependent model, looking ahead requires knowledge of future covariates.
  - you don't know them
  - so you have to guess
  - This is very, very hard to do effectively.

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  - This is very, very hard to do effectively.
  - Internal and external covariates

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