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casebase: An Alternative Framework For Survival Analysis

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Abstract

The abstract of the article. * joint co-authors

Keywords: keywords, not capitalized, Java.

1. Code formatting

Don't use markdown, instead use the more precise latex commands:

- Java
- **plyr**
- `print("abc")`

2. Introduction

- Motivation
  - Flexible
  - Flexible
  - Flexible

3. Theoretical details

4. Implementation details

1. Population-tim plots
2. Sampling
3. Fitting
4. Absolute Risks

5. Population-time plots

6. Case study 1: Veteran data (or ERSPC if we can)

- First example
- Show how we can test for non-proportional hazard?

7. Case study 2: Bone-marrow transplant

We will use the same data that was used in Scrucca *et al* (Scrucca, Santucci, and Aversa 2010). The data is available on the main author's website; it is also available as part of this package.

```
R> library(casebase)
```

```
See example usage at http://sahirbhatnagar.com/casebase/
```

```
R> library(magrittr)
R> library(tidyverse)
```

```
Loading tidyverse: ggplot2
Loading tidyverse: tibble
Loading tidyverse: tidyr
Loading tidyverse: readr
Loading tidyverse: purrr
Loading tidyverse: dplyr
```

```
Conflicts with tidy packages ----------------------------------------------
```

```
filter(): dplyr, stats
lag():    dplyr, stats
```

```
R> data(bmtcrr)
R> head(bmtcrr) %>% knitr::kable(format = "latex")
```

Sex	D	Phase	Age	Status	Source	ftime
M	ALL	Relapse	48	2	BM+PB	0.67
F	AML	CR2	23	1	BM+PB	9.50
M	ALL	CR3	7	0	BM+PB	131.77
F	ALL	CR2	26	2	BM+PB	24.03
F	ALL	CR2	36	2	BM+PB	1.47
M	ALL	Relapse	17	2	BM+PB	2.23

We will perform a competing risk analysis on data from 177 patients who received a stem cell transplant for acute leukemia. The event of interest in relapse, but other competing causes (e.g. transplant-related death) need to be taken into account. We also want to take into account the effect of several covariates such as Sex, Disease (lymphoblastic or myeloblastic leukemia, abbreviated as ALL and AML, respectively), Phase at transplant (Relapse, CR1, CR2, CR3), Source of stem cells (bone marrow and peripheral blood, coded as BM+PB, or peripheral blood, coded as PB), and Age. Below, we reproduce their Table 1:

```
R> table1 <- tibble::tribble(
R+     ~Variable, ~Description, ~`Statistical summary`,
R+     "Sex", "Sex", "M=Male (100)",
R+     "", "", "F=Female (77)",
R+     "D", "Disease", "ALL (73)",
R+     "", "", "AML (104)",
R+     "Phase", "Phase", "CR1 (47)",
R+     "", "", "CR2 (45)",
R+     "", "", "CR3 (12)",
R+     "", "", "Relapse (73)",
R+     "Source", "Type of transplant", "BM+PB (21)",
R+     "", "", "PB (156)",
R+     "Age", "Age of patient (years)", "4-62",
R+     "", "", "30.47 (13.04)",
R+     "Ftime", "Failure time (months)", "0.13-131.77",
R+     "", "", "20.28 (30.78)",
R+     "Status", "Status indicator", "0=censored (46)",
R+     "", "", "1=relapse (56)",
R+     "", "", "2=competing event (75)"
R+ )
R>
R> knitr::kable(table1, format = "latex")
```

Variable	Description	Statistical summary
Sex	Sex	M=Male (100)
		F=Female (77)
D	Disease	ALL (73)
		AML (104)
Phase	Phase	CR1 (47)
		CR2 (45)
		CR3 (12)
		Relapse (73)
Source	Type of transplant	BM+PB (21)
		PB (156)
Age	Age of patient (years)	4–62
		30.47 (13.04)
Ftime	Failure time (months)	0.13–131.77
		20.28 (30.78)
Status	Status indicator	0=censored (46)
		1=relapse (56)
		2=competing event (75)

The statistical summary is generated differently for continuous and categorical variables:

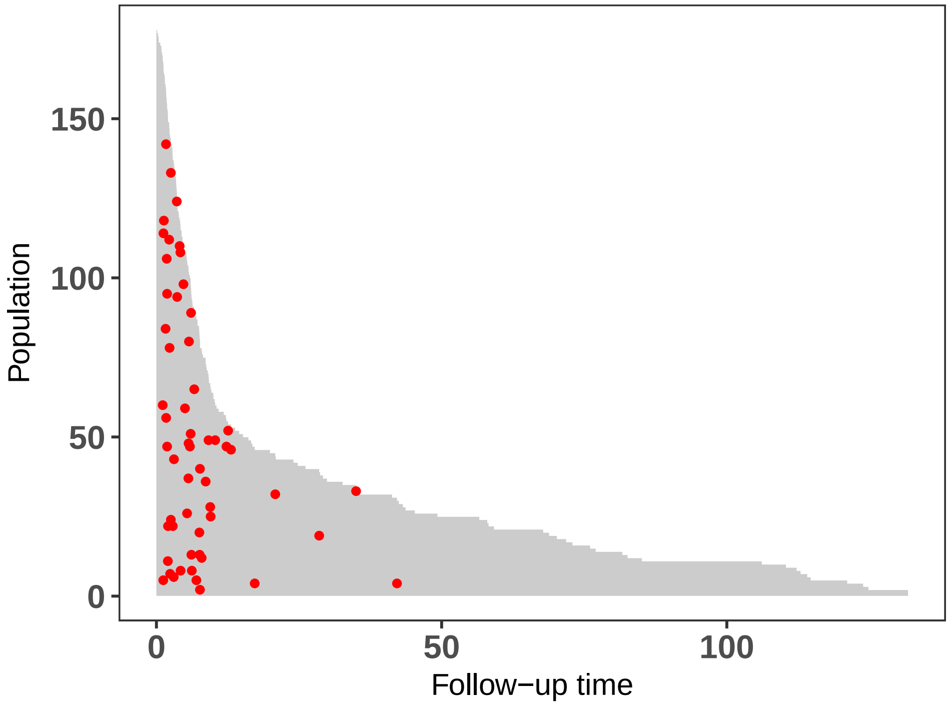
- For continuous variables, we are given the range, followed by the mean and standard deviation.

- For categorical variables, we are given the counts for each category.

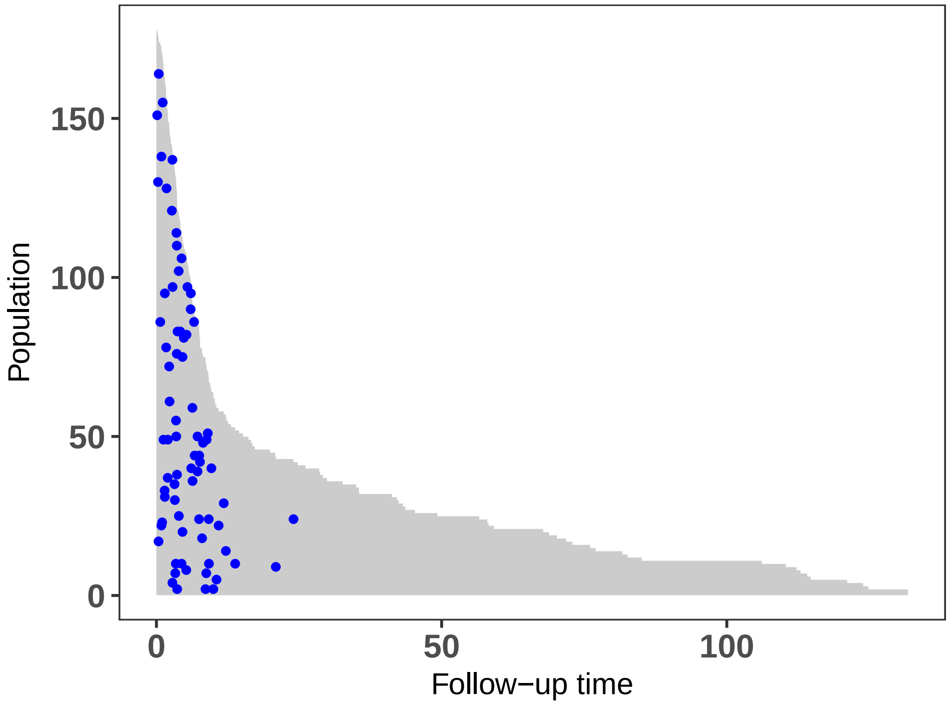
Note that failure time can also correspond to censoring.

In order to try and visualize the incidence density of relapse, we can look at a population-time plot: on the X-axis we have time, and on the Y-axis we have the size of the risk set at a particular time point. Failure times associated to the event of interest can then be highlighted on the plot using red dots.

```
R> pt_object <- casebase::popTime(bmtcrr, event = "Status", time = "ftime")
R> plot(pt_object)
```



```
R> pt_object_comp <- bmtcrr %>%
R+     mutate(Status = case_when(Status == 1 ~ 2L,
R+                               Status == 2 ~ 1L,
R+                               TRUE ~ Status)) %>%
R+     casebase::popTime(event = "Status", time = "ftime")
R> plot(pt_object_comp, point.colour = "blue")
```



From this last plot, we can see that there is no censoring during the first 10 months. Moreover, we see that the last competing event occurs around 20 months. Putting all this information together, we have evidence of two types of patients: very sick patients who either relapse or have a competing event early on, and healthier patients who are eventually lost to follow-up.

We now turn to the analysis of this dataset. The population-time plots above give evidence of non-constant hazard; therefore, we will explicitely include time in the model. Note that we also include all other variables as possible confounders. First, we include time as a linear term:

```
R> model1 <- fitSmoothHazard(Status ~ ftime + Sex + D + Phase + Source + Age,
R+                           data = bmtcrr,
R+                           ratio = 100,
R+                           time = "ftime")
R> summary(model1)
```

```
Call:
vglm(formula = formula, family = multinomial(refLevel = 1), data = sampleData)


Pearson residuals:
                       Min       1Q   Median        3Q   Max
log(mu[,2]/mu[,1]) -0.2324 -0.06980 -0.03900 -0.014615 45.18
log(mu[,3]/mu[,1]) -0.3028 -0.09008 -0.03748 -0.008052 19.79

Coefficients:
                Estimate Std. Error z value Pr(>|z|)
(Intercept):1  -3.473159   0.684472  -5.074 3.89e-07 ***
(Intercept):2  -2.483719   0.465134  -5.340 9.31e-08 ***
ftime:1        -0.069515   0.014754  -4.712 2.46e-06 ***
ftime:2        -0.104482   0.018274  -5.717 1.08e-08 ***
SexM:1         -0.298211   0.282266  -1.056 0.290744
SexM:2         -0.443015   0.236317  -1.875 0.060839 .
DAML:1         -0.580429   0.301271  -1.927 0.054029 .
DAML:2         -0.114156   0.274610  -0.416 0.677629
PhaseCR2:1      0.119138   0.466642   0.255 0.798485
PhaseCR2:2      0.213409   0.331729   0.643 0.520015
PhaseCR3:1      0.446436   0.690259   0.647 0.517783
PhaseCR3:2      0.151515   0.526646   0.288 0.773577
PhaseRelapse:1  1.361336   0.390162   3.489 0.000485 ***
PhaseRelapse:2  0.657054   0.307296   2.138 0.032502 *
SourcePB:1      0.570967   0.564054   1.012 0.311415
SourcePB:2     -0.941242   0.352134  -2.673 0.007518 **
Age:1          -0.008575   0.011883  -0.722 0.470504
Age:2           0.024955   0.009868   2.529 0.011442 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Number of linear predictors:  2

Names of linear predictors: log(mu[,2]/mu[,1]), log(mu[,3]/mu[,1])

Residual deviance: 1412.245 on 26444 degrees of freedom

Log-likelihood: -706.1222 on 26444 degrees of freedom

Number of iterations: 10

Reference group is level  1  of the response
```

Because of the results in Turgeon *et al* (Turgeon, Bhatnagar, Hanley, and Saarela), the standard errors we obtain from the multinomial logit fit are asymptotically correct, and therefore can be used to construct asymptotic confidence intervals.

From this summary, we see that time is indeed significant, as is Phase (only relapse vs. CR1). Interestingly, we see that the type of disease is only significant for the event of interest, whereas the type of transplant and the age of the patient are only significant for the competing event.

Next, we include the logarithm of time in the model (which leads to a Weibull hazard):

```
R> model2 <- fitSmoothHazard(Status ~ log(ftime) + Sex + D + Phase + Source + Age,
R+                           data = bmtcrr,
R+                           ratio = 100,
R+                           time = "ftime")
R> summary(model2)


Call:
vglm(formula = formula, family = multinomial(refLevel = 1), data = sampleData)


Pearson residuals:
                       Min       1Q   Median       3Q   Max
log(mu[,2]/mu[,1]) -0.4301 -0.06839 -0.04673 -0.03529 29.47
log(mu[,3]/mu[,1]) -0.6313 -0.07728 -0.05488 -0.04460 22.07

Coefficients:
                Estimate Std. Error z value Pr(>|z|)
(Intercept):1  -3.867645   0.712859  -5.426 5.78e-08 ***
(Intercept):2  -2.915708   0.470010  -6.203 5.52e-10 ***
log(ftime):1   -0.345600   0.071298  -4.847 1.25e-06 ***
log(ftime):2   -0.426302   0.057776  -7.379 1.60e-13 ***
SexM:1         -0.410838   0.293247  -1.401 0.161215
SexM:2         -0.482041   0.243193  -1.982 0.047465 *
DAML:1         -0.689708   0.302498  -2.280 0.022605 *
```

```
DAML:2         -0.165629   0.285741  -0.580 0.562152
PhaseCR2:1      0.264372   0.466874   0.566 0.571216
PhaseCR2:2      0.389075   0.330864   1.176 0.239620
PhaseCR3:1      0.416963   0.717569   0.581 0.561189
PhaseCR3:2      0.035184   0.539420   0.065 0.947994
PhaseRelapse:1  1.497807   0.391712   3.824 0.000131 ***
PhaseRelapse:2  0.900626   0.306158   2.942 0.003264 **
SourcePB:1      0.525555   0.606178   0.867 0.385942
SourcePB:2     -1.129794   0.370857  -3.046 0.002316 **
Age:1          -0.002345   0.011604  -0.202 0.839836
Age:2           0.029056   0.009815   2.960 0.003072 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Number of linear predictors:  2

Names of linear predictors: log(mu[,2]/mu[,1]), log(mu[,3]/mu[,1])

Residual deviance: 1502.709 on 26444 degrees of freedom

Log-likelihood: -751.3548 on 26444 degrees of freedom

Number of iterations: 8

Reference group is level  1  of the response
```

As we can see, the results are similar to the ones with a Gompertz hazard, although Sex is now significant for the competing event.

Finally, using splines, we can be quite flexible about the way the hazard depends on time:

```
R> model3 <- fitSmoothHazard(
R+     Status ~ splines::bs(ftime) + Sex + D + Phase + Source + Age,
R+     data = bmtcrr,
R+     ratio = 100,
R+     time = "ftime")
R> summary(model3)
```

```


Call:
vglm(formula = formula, family = multinomial(refLevel = 1), data = sampleData)


Pearson residuals:
                       Min       1Q   Median         3Q   Max
log(mu[,2]/mu[,1]) -0.2032 -0.07093 -0.03950 -6.478e-03 57.42
log(mu[,3]/mu[,1]) -0.2714 -0.09462 -0.01215 -3.633e-06 37.16
```

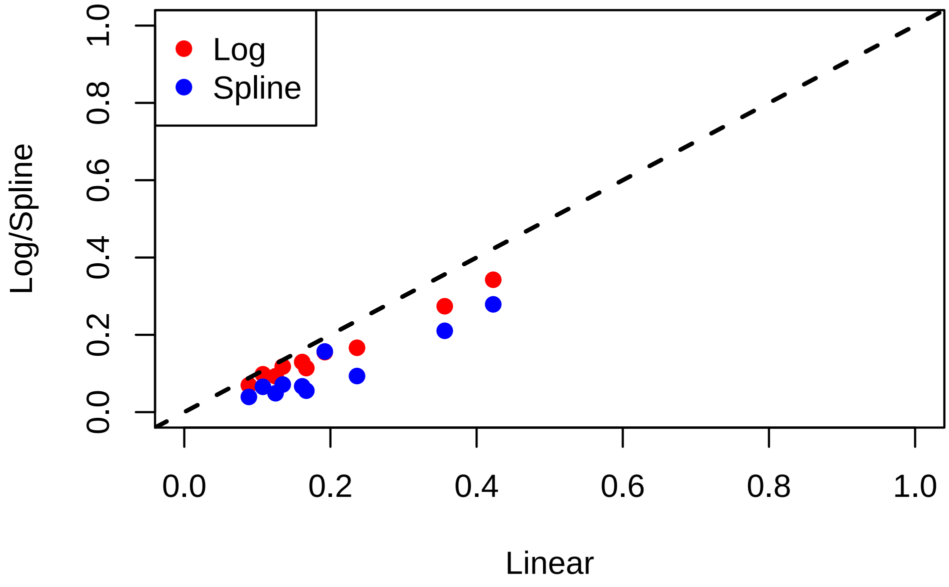
```
Coefficients:
                        Estimate Std. Error z value Pr(>|z|)    
(Intercept):1          -3.800875   0.713833  -5.325 1.01e-07 ***
(Intercept):2          -3.255436   0.515685  -6.313 2.74e-10 ***
splines::bs(ftime)1:1   0.603866   2.311386   0.261 0.793894    
splines::bs(ftime)1:2   8.064772   3.745888   2.153 0.031321 *  
splines::bs(ftime)2:1 -17.868972   8.390698  -2.130 0.033203 *  
splines::bs(ftime)2:2 -82.148252  26.046430  -3.154 0.001611 ** 
splines::bs(ftime)3:1  -2.012019   9.340686  -0.215 0.829453    
splines::bs(ftime)3:2  -2.790995  22.345501  -0.125 0.900601    
SexM:1                 -0.277399   0.284388  -0.975 0.329349    
SexM:2                 -0.418228   0.237149  -1.764 0.077805 .  
DAML:1                 -0.649732   0.304770  -2.132 0.033017 *  
DAML:2                 -0.143387   0.278769  -0.514 0.607001    
PhaseCR2:1              0.176145   0.467658   0.377 0.706431    
PhaseCR2:2              0.340090   0.332192   1.024 0.305941    
PhaseCR3:1              0.540857   0.697533   0.775 0.438112    
PhaseCR3:2              0.241321   0.529642   0.456 0.648656    
PhaseRelapse:1          1.503814   0.395120   3.806 0.000141 ***
PhaseRelapse:2          0.874907   0.314308   2.784 0.005376 ** 
SourcePB:1              0.444475   0.576583   0.771 0.440779    
SourcePB:2             -1.174262   0.360405  -3.258 0.001121 ** 
Age:1                  -0.005234   0.011979  -0.437 0.662179    
Age:2                   0.028974   0.010077   2.875 0.004039 ** 
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Number of linear predictors:  2 

Names of linear predictors: log(mu[,2]/mu[,1]), log(mu[,3]/mu[,1])

Residual deviance: 1393.424 on 26440 degrees of freedom

Log-likelihood: -696.7122 on 26440 degrees of freedom

Number of iterations: 16 

Reference group is level  1  of the response
```

Again, we see that the results are quite similar for this third model.

We now look at the 2-year risk of relapse:

```
R> linearRisk <- absoluteRisk(object = model1, time = 24, newdata = bmtcrr[1:10,])
R> logRisk <- absoluteRisk(object = model2, time = 24, newdata = bmtcrr[1:10,])
R> splineRisk <- absoluteRisk(object = model3, time = 24, newdata = bmtcrr[1:10,])
```

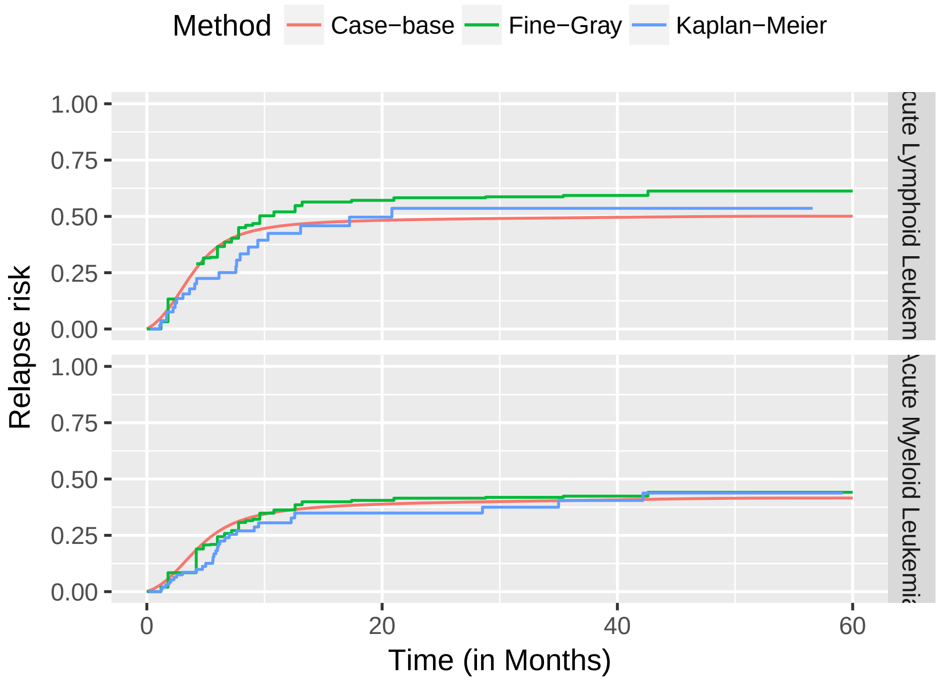
```
R> plot(linearRisk, logRisk,
R+      xlab = "Linear", ylab = "Log/Spline", pch = 19,
R+      xlim = c(0,1), ylim = c(0,1), col = 'red')
R> points(linearRisk, splineRisk,
R+        col = 'blue', pch = 19)
R> abline(a = 0, b = 1, lty = 2, lwd = 2)
R> legend("topleft", legend = c("Log", "Spline"),
R+        pch = 19, col = c("red", "blue"))
```



We can also estimate the mean absolute risk for the entire dataset:

```
R> mean(linearRisk)

[1] 0.1991813

R> mean(logRisk)

[1] 0.1560315

R> mean(splineRisk)

[1] 0.1087245

R> # Absolute risks----
R> library(tidyverse)
R> library(magrittr)
R> library(splines)
R> library(survival)
R> library(timereg)
```

```
R>
R> bmtcrr %<>% filter(Age >= 16)
R>
R> bmtcrr %>% select(Sex) %>% table

.
 F  M
72 87

R> bmtcrr %>% select(D) %>% table

.
ALL AML
 59 100

R> bmtcrr %>% select(Phase) %>% table

.
    CR1     CR2     CR3 Relapse
     44      40      10      65

R> bmtcrr %>% select(Source) %>% table

.
BM+PB    PB
   15   144

R> bmtcrr %>% select(Status) %>% table

.
 0  1  2
40 49 70

R> model_cb <- fitSmoothHazard(Status ~ bs(ftime, df = 5) + Sex + D + Phase + Source + Age
R+                             data = bmtcrr, time = "ftime")
R> model_fg <- comp.risk(Event(ftime, Status) ~ const(Sex) + const(D) +
R+                           const(Phase) + const(Source) + const(Age),
R+                       data = bmtcrr, cause = 1, model = "fg")
R> model_cox <- coxph(Surv(ftime, Status == 1) ~ Sex + D + Phase + Source + Age,
R+                    data = bmtcrr)
R>
R> time_points <- (0:100)*60/100
R>
R> # ALL vs. AML
R> newdata <- data.frame("Sex" = factor(c("F", "F"),
R+                                      levels = c("F", "M")),
R+                       "D" = c("ALL", "AML"),
R+                       "Phase" = factor(c("Relapse", "Relapse"),
R+                                        levels = c("CR1", "CR2", "CR3", "Relapse")),
R+                       "Age" = c(35, 35),
R+                       "Source" = factor(c("PB", "PB"),
R+                                         levels = c("BM+PB", "PB")))
R>
R> risk_cb <- absoluteRisk(object = model_cb, time = time_points,
R+                         method = "montecarlo", newdata = newdata)
R> risk_cb <- bind_rows(data.frame(Time = time_points, Method = "Case-base", Risk = risk_c
R+                                 stringsAsFactors = FALSE),
R+                      data.frame(Time = time_points, Method = "Case-base", Risk = risk_c
R+                                 stringsAsFactors = FALSE))
R>
R> risk_fg <- predict(model_fg, newdata, times = time_points)
R> risk_fg <- bind_rows(data.frame(Time = time_points, Method = "Fine-Gray", Risk = risk_f
R+                                 stringsAsFactors = FALSE),
R+                      data.frame(Time = time_points, Method = "Fine-Gray", Risk = risk_f
R+                                 stringsAsFactors = FALSE))
R> risk_km <- map_df(c("ALL", "AML"), function(disease) {
R+     foo <- bmtcrr %>%
R+         filter(D == disease) %>%
R+         survfit(Surv(ftime,Status == 1) ~ 1, data = .)
R+     data.frame(Time = foo$time, Method = "Kaplan-Meier", Risk = 1 - foo$surv, Disease =
R+                stringsAsFactors = FALSE) %>%
R+         filter(Time <= 60)
R+ })
R>
R> disease_names <- c("ALL" = "Acute Lymphoid Leukemia",
R+                    "AML" = "Acute Myeloid Leukemia")
R> risk_cb %>%
R+     bind_rows(risk_fg,
R+               risk_km) %>%
R+     arrange(Disease, Risk) %>%
R+     ggplot(aes(Time, Risk, colour = Method)) +
R+     geom_line(data = . %>% filter(Method == "Case-base")) +
R+     geom_step(data = . %>% filter(Method != "Case-base")) +
R+     facet_grid(Disease ~ ., labeller = as_labeller(disease_names)) + ylim(c(0,1)) +
R+     theme(legend.position = "top") +
R+     xlab("Time (in Months)") + ylab("Relapse risk")
```



\begin{CodeChunk}

\begin{CodeInput} R> # Table of coefficients—- R> z_value <- qnorm(0.975) R> table_cb <- summary(model_cb)**?**, seq(13, 25, by = 2), 1:2 R> table_cb <- cbind(table_cb[,1], R+ table_cb[,1] - z_value * table_cb[,2], R+ table_cb[,1] + z_value * table_cb[,2]) R> table_cb <- round(exp(table_cb), 2) R> R> table_cox <- round(summary(model_cox)$conf.int[,-2], 2) \end{CodeInput} \end{CodeChunk}

8. Case study 3: Vaccination study (recurrent events)

- Give a more complex example of sampling; time-dependent exposure
  - Sampling needs to be done manually, but fitting function can still be used

9. Discussion

References

References

Scrucca L, Santucci A, Aversa F (2010). "Regression modeling of competing risk using R: an in depth guide for clinicians." *Bone marrow transplantation*, **45**(9), 1388.

Turgeon M, Bhatnagar S, Hanley J, Saarela O (????). "A novel approach to competing risks using case-base sampling." (In preparation).

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