Tutorial in biostatistics: Competing risks and multi-state models
Analyses using the *mstate* package

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1 Introduction

This is a companion file both for the *mstate* package and for the Tutorial in Biostatistics: Competing risks and multi-state models (Putter et al. 2007), simply referred to henceforth as the tutorial. Emphasis in this document will be on the use of *mstate*, not on the theory of competing risks and multi-state models. The only exception is that I have added some theory about the Aalen-Johansen estimator that is implemented in *mstate* but did not appear in the tutorial. For other theory on multi-state models, and for interpretation of the results of the analyses, we will repeatedly refer to the tutorial. I will occasionally give more detail and show more analyses than in the tutorial. Also I sometimes give more details on the function in *mstate* than strictly necessary for the analyses in the tutorial, but not all features will be shown either. This file and the *mstate* package, which in turn contains all the data used in the tutorial, can be found at `http://www.msbi.nl/multistate`. This file is also a vignette of the *mstate* package. Type `vignette("Tutorial")` after having installed and loaded *mstate* to access this document within R.

I do not follow the order of the tutorial. Rather, I will start with multi-state models, Section 4 of the tutorial, and finally switch back to the special case of competing risks models. Sections 2, 3 and 4 of this document will discuss data preparation, estimation and prediction, respectively in multi-state models. In Section 5 I illustrate some functions of *mstate* designed especially for competing risks.

After installation, the *mstate* package is loaded in the usual way.

```
> library(mstate)
```

The versions of R and *mstate* used in this document are as follows:

```
> R.version$version.string
```

```
[1] "R version 4.0.4 (2021-02-15)"
```

```
> packageDescription("mstate", fields = "Version")
```

```
[1] "0.3.2"
```

2 Data preparation

The data used in Section 4 of the tutorial are 2204 patients transplanted at the EBMT between 1995 and 1998. These data are included in the *mstate* package. For (a tiny bit) more background on the data, refer to the tutorial, or type `help(ebmt3)`.

```
> data(ebmt3)
> head(ebmt3)
```

```
  id prtime prstat rfstime rfsstat dissub  age              drmatch    tcd
1  1     23      1     744       0    CML  >40     Gender mismatch No TCD
2  2     35      1     360       1    CML  >40  No gender mismatch No TCD
3  3     26      1     135       1    CML  >40  No gender mismatch No TCD
4  4     22      1     995       0    AML 20-40 No gender mismatch No TCD
5  5     29      1     422       1    AML 20-40 No gender mismatch No TCD
6  6     38      1     119       1    ALL  >40  No gender mismatch No TCD
```

Let us first have a look at the covariates. For instance disease subclassification:

```
> n <- nrow(ebmt3)
> table(ebmt3$dissub)

AML ALL CML
853 447 904

> round(100 * table(ebmt3$dissub)/n)

AML ALL CML
 39  20  41
```

The output of the other covariates is omitted.

```
> table(ebmt3$age)
> round(100 * table(ebmt3$age)/n)
> table(ebmt3$drmatch)
> round(100 * table(ebmt3$drmatch)/n)
> table(ebmt3$tcd)
> round(100 * table(ebmt3$tcd)/n)
```

The first step in a multi-state model analysis is to set up the transition matrix. The transition matrix specifies which direct transitions are possible (those with NA are impossible) and assigns numbers to the transitions for future reference. This can be done explicitly.

```
> tmat <- matrix(NA, 3, 3)
> tmat[1, 2:3] <- 1:2
> tmat[2, 3] <- 3
> dimnames(tmat) <- list(from = c("Tx", "PR", "RelDeath"), to = c("Tx",
+     "PR", "RelDeath"))
> tmat

          to
from       Tx PR RelDeath
  Tx       NA  1        2
  PR       NA NA        3
  RelDeath NA NA       NA
```

Steven McKinney has kindly provided a convenient function *transMat* to define transition matrices. The same transition matrix may be constructed as follows.

```
> tmat <- transMat(x = list(c(2, 3), c(3), c()), names = c("Tx",
+     "PR", "RelDeath"))
> tmat

          to
from       Tx PR RelDeath
  Tx       NA  1        2
  PR       NA NA        3
  RelDeath NA NA       NA
```

For common multi-state models, such as the illness-death model (and competing risks models, Section 5) there is a built-in function to obtain these transition matrices more easily.

```
> tmat <- trans.illdeath(names = c("Tx", "PR", "RelDeath"))
> tmat
```

```
          to
from       Tx PR RelDeath
  Tx       NA  1        2
  PR       NA NA        3
  RelDeath NA NA       NA
```

The function *paths* can be used to give a list of all possible paths through the multi-state model. This function should not be used for transition matrices specifying a multi-state model with loops, since there will be infinitely many paths. At the moment there is no check for the presence of loops, but this will be included shortly.

```
> paths(tmat)
```

```
     [,1] [,2] [,3]
[1,]    1   NA   NA
[2,]    1    2   NA
[3,]    1    2    3
[4,]    1    3   NA
```

Time in the `ebmt3` data is reported in days; before doing any analysis, we first convert this to years.

```
> ebmt3$prtime <- ebmt3$prtime/365.25
> ebmt3$rfstime <- ebmt3$rfstime/365.25
```

In order to prepare data in long format, we specify the names of the covariates that we are interested in modeling. Note that I am adding `prtime`, which is not really a covariate, but specifying the time of platelet recovery. The purpose of this will become clear later. The specified covariates are to be retained in the dataset in long format (this is the argument *keep*), which we are going to call `msbmt`. For the original dataset `ebmt3`, each row corresponds to a single patient. For the long format data `msbmt`, each row will correspond to a transition for which a patient is at risk. See the tutorial for more detailed information.

```
> covs <- c("dissub", "age", "drmatch", "tcd", "prtime")
> msbmt <- msprep(time = c(NA, "prtime", "rfstime"), status = c(NA,
+     "prstat", "rfsstat"), data = ebmt3, trans = tmat, keep = covs)
```

The result is an S3 object of class *msdata* and *data.frame*. An *msdata* object is actually only a data frame with a `trans` attribute holding the transition matrix used to define it. A *print* method has been defined for *msdata* objects, which also prints the transition matrix if requested (set argument *trans* to TRUE, default is FALSE).

```
> head(msbmt)
```

```
An object of class 'msdata'
```

```
Data:
  id from to trans      Tstart       Tstop       time status dissub age
1  1    1  2     1 0.00000000 0.06297057 0.06297057      1    CML >40
```

```
2 1    1 3    2 0.00000000 0.06297057 0.06297057      0    CML >40
3 1    2 3    3 0.06297057 2.03696099 1.97399042      0    CML >40
4 2    1 2    1 0.00000000 0.09582478 0.09582478      1    CML >40
5 2    1 3    2 0.00000000 0.09582478 0.09582478      0    CML >40
6 2    2 3    3 0.09582478 0.98562628 0.88980151      1    CML >40
            drmatch    tcd    prtime
1    Gender mismatch No TCD 0.06297057
2    Gender mismatch No TCD 0.06297057
3    Gender mismatch No TCD 0.06297057
4 No gender mismatch No TCD 0.09582478
5 No gender mismatch No TCD 0.09582478
6 No gender mismatch No TCD 0.09582478
```

In the above call of *msprep*, the *time* and *status* arguments specify the column names in the data `ebmt3` corresponding to the three states in the multi-state model. Since all the patients start in state 1 at time 0, the *time* and *status* arguments corresponding to the first state do not really have a value. In such cases, the corresponding elements of *time* and *status* may be given the value `NA`. An alternative way of specifying *time* and *status* (and *keep* as well) is as matrices of dimension $n \times S$ with S the number of states (and $n \times p$ with p the number of covariates for *keep*). The *data* argument doesn't need to be specified then.

The number of events in the data can be summarized with the function *events*.

```
> events(msbmt)

$Frequencies
          to
from        Tx   PR RelDeath no event total entering
  Tx         0 1169      458      577          2204
  PR         0    0      383      786          1169
  RelDeath   0    0        0      841           841


$Proportions
          to
from             Tx        PR  RelDeath  no event
  Tx      0.0000000 0.5303993 0.2078040 0.2617967
  PR      0.0000000 0.0000000 0.3276305 0.6723695
  RelDeath 0.0000000 0.0000000 0.0000000 1.0000000
```

For regression purposes, we now add transition-specific covariates to the dataset. For more details on transition-specific covariates, refer to the tutorial. For a numerical covariate `cov`, the names of the expanded (transition-specific) covariates are `cov.1`, `cov.2` etc. The extension `.i` refers to transition number i. First, we define these transition-specific covariates as a separate dataset, by setting *append* to `FALSE`.

```
> expcovs <- expand.covs(msbmt, covs[2:3], append = FALSE)
> head(expcovs)

  age20.40.1 age20.40.2 age20.40.3 age.40.1 age.40.2 age.40.3
1          0          0          0        1        0        0
2          0          0          0        0        1        0
3          0          0          0        0        0        1
```

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```
4              0            0            0           1           0           0
5              0            0            0           0           1           0
6              0            0            0           0           0           1
  drmatchGender.mismatch.1 drmatchGender.mismatch.2 drmatchGender.mismatch.3
1                        1                        0                        0
2                        0                        1                        0
3                        0                        0                        1
4                        0                        0                        0
5                        0                        0                        0
6                        0                        0                        0
```

We see that this expanded covariates dataset is quite large, and that the covariate names are quite long. For categorical covariates, the default names of the expanded covariates are a combination of the covariate name, the level (similar to the names of the regression coefficients that you see in regression output), followed by the transition number, in such a way that the combination is allowed as column name. If these names are too long, the user may set the value of *longnames* (default=TRUE) to `FALSE`. In this case, the covariate name is followed by 1, 2 etc, before the transition number. In case of a covariate with only two levels, the covariate name is just followed by the transition number. Confident that this will work out, we also set *append* to `TRUE` (default), which will append the expanded covariates to the dataset.

```
> msbmt <- expand.covs(msbmt, covs, append = TRUE, longnames = FALSE)
> head(msbmt)

An object of class 'msdata'

Data:
  id from to trans      Tstart       Tstop       time status dissub age
1  1    1  2     1 0.00000000 0.06297057 0.06297057      1    CML >40
2  1    1  3     2 0.00000000 0.06297057 0.06297057      0    CML >40
3  1    2  3     3 0.06297057 2.03696099 1.97399042      0    CML >40
4  2    1  2     1 0.00000000 0.09582478 0.09582478      1    CML >40
5  2    1  3     2 0.00000000 0.09582478 0.09582478      0    CML >40
6  2    2  3     3 0.09582478 0.98562628 0.88980151      1    CML >40
            drmatch    tcd     prtime dissub1.1 dissub1.2 dissub1.3 dissub2.1
1    Gender mismatch No TCD 0.06297057         0         0         0         1
2    Gender mismatch No TCD 0.06297057         0         0         0         0
3    Gender mismatch No TCD 0.06297057         0         0         0         0
4 No gender mismatch No TCD 0.09582478         0         0         0         1
5 No gender mismatch No TCD 0.09582478         0         0         0         0
6 No gender mismatch No TCD 0.09582478         0         0         0         0
  dissub2.2 dissub2.3 age1.1 age1.2 age1.3 age2.1 age2.2 age2.3 drmatch.1
1         0         0      0      0      0      1      0      0         1
2         1         0      0      0      0      0      1      0         0
3         0         1      0      0      0      0      0      1         0
4         0         0      0      0      0      1      0      0         0
5         1         0      0      0      0      0      1      0         0
6         0         1      0      0      0      0      0      1         0
  drmatch.2 drmatch.3 tcd.1 tcd.2 tcd.3    prtime.1    prtime.2    prtime.3
1         0         0     0     0     0 0.06297057 0.00000000 0.00000000
```

6

```
2          1         0    0    0      0 0.00000000 0.06297057 0.00000000
3          0         1    0    0      0 0.00000000 0.00000000 0.06297057
4          0         0    0    0      0 0.09582478 0.00000000 0.00000000
5          0         0    0    0      0 0.00000000 0.09582478 0.00000000
6          0         0    0    0      0 0.00000000 0.00000000 0.09582478
```

The names indeed are quite a bit shorter. The downside however is that we need to remember for ourselves to which category for instance the number 1 in `age1.2` corresponds (age 20-40 with ≤ 20 as reference category).

3 Estimation

After having prepared the data in long format, estimation of covariate effects using Cox regression is straightforward using the *coxph* function of the *survival* package. This is not at all a feature of the *mstate* package, other than that *msprep* has facilitated preparation of the data. Let us consider the Markov model, where we assume different effects of the covariates for different transitions; hence we use the transition-specific covariates obtained by *expand.covs*. The delayed entry aspect of this model for transition 3 (see discussion in the tutorial) is achieved by specifying *Surv(Tstart,Tstop,status)*, where (this is reflected in the long format data) `Tstart` is the time of entry in the state, and `Tstop` the event or censoring time, depending on the value of `status`. We consider first the model without any proportionality assumption on the baseline hazards; this is achieved by adding *strata(trans)* to the formula, which estimates separate baseline hazards for different values of `trans` (the transitions). The results appear in the left column of Table III of the tutorial.

```
> c1 <- coxph(Surv(Tstart, Tstop, status) ~ dissub1.1 + dissub2.1 +
+     age1.1 + age2.1 + drmatch.1 + tcd.1 + dissub1.2 + dissub2.2 +
+     age1.2 + age2.2 + drmatch.2 + tcd.2 + dissub1.3 + dissub2.3 +
+     age1.3 + age2.3 + drmatch.3 + tcd.3 + strata(trans), data = msbmt,
+     method = "breslow")
> c1

Call:
coxph(formula = Surv(Tstart, Tstop, status) ~ dissub1.1 + dissub2.1 +
    age1.1 + age2.1 + drmatch.1 + tcd.1 + dissub1.2 + dissub2.2 +
    age1.2 + age2.2 + drmatch.2 + tcd.2 + dissub1.3 + dissub2.3 +
    age1.3 + age2.3 + drmatch.3 + tcd.3 + strata(trans), data = msbmt,
    method = "breslow")

             coef exp(coef) se(coef)      z        p
dissub1.1 -0.04359   0.95734  0.07789 -0.560 0.575698
dissub2.1 -0.29724   0.74287  0.06800 -4.371 1.23e-05
age1.1    -0.16461   0.84822  0.07905 -2.082 0.037317
age2.1    -0.08979   0.91412  0.08647 -1.038 0.299075
drmatch.1  0.04575   1.04681  0.06660  0.687 0.492127
tcd.1      0.42907   1.53583  0.08043  5.335 9.57e-08
dissub1.2  0.25589   1.29161  0.13520  1.893 0.058411
dissub2.2  0.01675   1.01689  0.10838  0.155 0.877188
age1.2     0.25516   1.29067  0.15103  1.689 0.091127
age2.2     0.52649   1.69298  0.15790  3.334 0.000855
```

```
drmatch.2 -0.07525   0.92751   0.11028 -0.682 0.495006
tcd.2       0.29673   1.34545   0.15007  1.977 0.048006
dissub1.3 0.13646   1.14621   0.14804  0.922 0.356634
dissub2.3 0.24692   1.28007   0.11685  2.113 0.034596
age1.3      0.06156   1.06350   0.15343  0.401 0.688239
age2.3      0.58075   1.78737   0.16014  3.627 0.000287
drmatch.3 0.17280   1.18863   0.11452  1.509 0.131315
tcd.3       0.20088   1.22248   0.12636  1.590 0.111873


Likelihood ratio test=117.7  on 18 df, p=< 2.2e-16
n= 5577, number of events= 2010
```

The interpretation is discussed in the tutorial.

The next model considered is the Markov model where the transition hazards into relapse or death (these correspond to transitions 2 and 3) are assumed to be proportional. For this purpose transition 1 (transplantation → platelet recovery) belongs to one stratum and transitions 2 (transplantation → relapse/death) and 3 (platelet recovery → relapse/death) belong to a second stratum. Transitions 2 and 3 have the same receiving state, hence the same value of `to`, so the two strata can be distinguished by the variable `to` in our dataset. In order to distinguish between transitions 2 and 3, we introduce a time-dependent covariate `pr` that indicates whether or not platelet recovery has already occurred. For transition 2 (Tx → RelDeath) the value of `pr` equals 0, while for transition 3 (PR → RelDeath) the value of `pr` equals 1. Results are found in the middle of Table III of the tutorial.

```
> msbmt$pr <- 0
> msbmt$pr[msbmt$trans == 3] <- 1
> c2 <- coxph(Surv(Tstart, Tstop, status) ~ dissub1.1 + dissub2.1 +
+     age1.1 + age2.1 + drmatch.1 + tcd.1 + dissub1.2 + dissub2.2 +
+     age1.2 + age2.2 + drmatch.2 + tcd.2 + dissub1.3 + dissub2.3 +
+     age1.3 + age2.3 + drmatch.3 + tcd.3 + pr + strata(to), data = msbmt,
+     method = "breslow")
> c2

Call:
coxph(formula = Surv(Tstart, Tstop, status) ~ dissub1.1 + dissub2.1 +
    age1.1 + age2.1 + drmatch.1 + tcd.1 + dissub1.2 + dissub2.2 +
    age1.2 + age2.2 + drmatch.2 + tcd.2 + dissub1.3 + dissub2.3 +
    age1.3 + age2.3 + drmatch.3 + tcd.3 + pr + strata(to), data = msbmt,
    method = "breslow")


               coef exp(coef)  se(coef)       z        p
dissub1.1 -0.043592  0.957345  0.077887 -0.560 0.575698
dissub2.1 -0.297240  0.742866  0.067996 -4.371 1.23e-05
age1.1    -0.164613  0.848222  0.079054 -2.082 0.037317
age2.1    -0.089790  0.914123  0.086468 -1.038 0.299075
drmatch.1 0.045751  1.046814  0.066602  0.687 0.492127
tcd.1      0.429071  1.535831  0.080432  5.335 9.57e-08
dissub1.2 0.260968  1.298186  0.135182  1.930 0.053546
dissub2.2 0.003637  1.003644  0.108368  0.034 0.973226
age1.2     0.250894  1.285174  0.151057  1.661 0.096727
```

```
age2.2      0.525790  1.691796  0.157895  3.330 0.000868
drmatch.2 -0.072067  0.930469  0.110260 -0.654 0.513364
tcd.2       0.318537  1.375114  0.149970  2.124 0.033669
dissub1.3 0.139811  1.150056  0.147981  0.945 0.344767
dissub2.3 0.250328  1.284447  0.116788  2.143 0.032078
age1.3      0.055559  1.057131  0.153372  0.362 0.717166
age2.3      0.562484  1.755027  0.159970  3.516 0.000438
drmatch.3 0.169149  1.184297  0.114446  1.478 0.139414
tcd.3       0.211029  1.234948  0.126198  1.672 0.094484
pr         -0.378633  0.684797  0.211523 -1.790 0.073449

Likelihood ratio test=135.3  on 19 df, p=< 2.2e-16
n= 5577, number of events= 2010
```

For a discussion of the results we again refer to the tutorial. The hazard ratio of `pr` (0.685) and its p-value (0.073) indicate a trend-significant beneficial effect of platelet recovery on relapse-free survival. Later on we will look at the corresponding baseline transition intensities for these two models and see as a graphical check that the assumption of proportionality of the baseline hazards for transitions 2 and 3 is reasonable. This can also be tested formally using the function *cox.zph* (part of the *survival* package, not of *mstate*).

```
> cox.zph(c2)

            chisq df       p
dissub1.1 2.46e+01  1 6.9e-07
dissub2.1 9.68e+00  1 0.00187
age1.1    1.05e-01  1 0.74633
age2.1    6.48e+00  1 0.01092
drmatch.1 6.99e+00  1 0.00821
tcd.1     1.41e+01  1 0.00017
dissub1.2 5.43e+00  1 0.01975
dissub2.2 4.43e+00  1 0.03535
age1.2    4.79e+00  1 0.02863
age2.2    1.46e+00  1 0.22647
drmatch.2 1.12e-01  1 0.73759
tcd.2     1.07e+00  1 0.30179
dissub1.3 4.93e-05  1 0.99440
dissub2.3 2.41e+01  1 9.4e-07
age1.3    2.64e+00  1 0.10394
age2.3    6.80e+00  1 0.00913
drmatch.3 4.65e+00  1 0.03109
tcd.3     1.83e+01  1 1.9e-05
pr        1.64e+01  1 5.2e-05
GLOBAL    1.17e+02 19 4.8e-16
```

There is no evidence of non-proportionality of the baseline transition intensities of transitions 2 (p=0.496 for `pr`). There is strong evidence that the proportional hazards assumption for `dissub2` (CML vs AML) is violated, at least for the transitions into relapse and death. This makes sense, clinically, since CML and AML are two diseases with completely different biological pathways. It would have been much better to study separate multi-state models for the three

disease subclassifications. However, since the purpose of this manuscript is to illustrate the use of *mstate*, we will blatantly ignore the clear evidence of non-proportionality for the disease subclassifications.

Building on the Markov PH model, we can investigate whether the time at which a patient arrived in state 2 (PR) influences the subsequent RFS rate, that is, the transition hazard of PR → RelDeath. Here the purpose of expanding `prtime` becomes apparent. Since `prtime` only makes sense for transition 3 (PR → RelDeath), we need the transition-specific covariate of `prtime` for transition 3, which is `prtime.3`. The corresponding model is termed the "state arrival extended Markov PH" model in the tutorial, and appears on the right of Table III.

```
> c3 <- coxph(Surv(Tstart, Tstop, status) ~ dissub1.1 + dissub2.1 +
+     age1.1 + age2.1 + drmatch.1 + tcd.1 + dissub1.2 + dissub2.2 +
+     age1.2 + age2.2 + drmatch.2 + tcd.2 + dissub1.3 + dissub2.3 +
+     age1.3 + age2.3 + drmatch.3 + tcd.3 + pr + prtime.3 + strata(to),
+     data = msbmt, method = "breslow")
> c3

Call:
coxph(formula = Surv(Tstart, Tstop, status) ~ dissub1.1 + dissub2.1 +
    age1.1 + age2.1 + drmatch.1 + tcd.1 + dissub1.2 + dissub2.2 +
    age1.2 + age2.2 + drmatch.2 + tcd.2 + dissub1.3 + dissub2.3 +
    age1.3 + age2.3 + drmatch.3 + tcd.3 + pr + prtime.3 + strata(to),
    data = msbmt, method = "breslow")


                coef exp(coef)  se(coef)       z         p
dissub1.1  -0.043592  0.957345  0.077887  -0.560  0.575698
dissub2.1  -0.297240  0.742866  0.067996  -4.371  1.23e-05
age1.1     -0.164613  0.848222  0.079054  -2.082  0.037317
age2.1     -0.089790  0.914123  0.086468  -1.038  0.299075
drmatch.1   0.045751  1.046814  0.066602   0.687  0.492127
tcd.1       0.429071  1.535831  0.080432   5.335  9.57e-08
dissub1.2   0.260899  1.298097  0.135182   1.930  0.053609
dissub2.2   0.003761  1.003768  0.108368   0.035  0.972315
age1.2      0.250952  1.285248  0.151056   1.661  0.096649
age2.2      0.525772  1.691764  0.157894   3.330  0.000869
drmatch.2  -0.072088  0.930449  0.110260  -0.654  0.513238
tcd.2       0.318238  1.374703  0.149971   2.122  0.033838
dissub1.3   0.132021  1.141132  0.148849   0.887  0.375109
dissub2.3   0.251811  1.286353  0.116823   2.155  0.031123
age1.3      0.058227  1.059956  0.153426   0.380  0.704306
age2.3      0.565752  1.760771  0.160011   3.536  0.000407
drmatch.3   0.166817  1.181538  0.114556   1.456  0.145334
tcd.3       0.207404  1.230480  0.126431   1.640  0.100911
pr         -0.406872  0.665729  0.219075  -1.857  0.063279
prtime.3    0.295226  1.343430  0.594952   0.496  0.619741


Likelihood ratio test=135.5  on 20 df, p=< 2.2e-16
n= 5577, number of events= 2010
```

The influence of the time at which platelet recovery occurred seems small and is not significant (p=0.62, last row).

The clock-reset models may be obtained very similarly to those of the clock-forward models. The only difference is that *Surv(Tstart,Tstop,status)* is replaced by *Surv(time,status)*. This reflects the fact (recall that in our long format data each row corresponds to a transition) that for each transition the time starts at 0, rather than `Tstart`, the time since start of study at which the state has been entered. We will only show the code, not the output; the reader may try this for him-or herself.

```
> c4 <- coxph(Surv(time, status) ~ dissub1.1 + dissub2.1 + age1.1 +
+     age2.1 + drmatch.1 + tcd.1 + dissub1.2 + dissub2.2 + age1.2 +
+     age2.2 + drmatch.2 + tcd.2 + dissub1.3 + dissub2.3 + age1.3 +
+     age2.3 + drmatch.3 + tcd.3 + strata(trans), data = msbmt,
+     method = "breslow")
> c5 <- coxph(Surv(time, status) ~ dissub1.1 + dissub2.1 + age1.1 +
+     age2.1 + drmatch.1 + tcd.1 + dissub1.2 + dissub2.2 + age1.2 +
+     age2.2 + drmatch.2 + tcd.2 + dissub1.3 + dissub2.3 + age1.3 +
+     age2.3 + drmatch.3 + tcd.3 + pr + strata(to), data = msbmt,
+     method = "breslow")
> c6 <- coxph(Surv(time, status) ~ dissub1.1 + dissub2.1 + age1.1 +
+     age2.1 + drmatch.1 + tcd.1 + dissub1.2 + dissub2.2 + age1.2 +
+     age2.2 + drmatch.2 + tcd.2 + dissub1.3 + dissub2.3 + age1.3 +
+     age2.3 + drmatch.3 + tcd.3 + pr + prtime.3 + strata(to),
+     data = msbmt, method = "breslow")
```

4 Prediction

In order to obtain prediction probabilities in the context of the Markov multi-state models discussed in the previous section, basically two steps are involved. The first is to use the estimated parameters and baseline transition hazards and the covariate values of a patient of interest, to obtain patient-specific transition hazards for that patient, for each of the transitions in the multi-state model. This is what the function `msfit` is designed to do. The second step is to use the resulting patient-specific transition hazards (and variances and covariances) as input for `probtrans` to obtain (patient-specific) transition probabilities.

I will first show how `msfit` can be used to obtain the baseline hazards associated with the Markov stratified and PH models. The hazards of the Markov stratified models (and their variances and covariates) are obtained by first creating a new dataset containing the (expanded) covariates along with their values (in this case 0). This is very similar to the use of `survfit` from the *survival* package. The important difference is that for one patient, this *newdata* data frame needs to have exactly one line for each transition. When transition-specific covariates have been used in the model, the easiest way to obtain such a data frame is to first create a data frame with the basic covariates and then using `expand.covs` to obtain the transition-specific covariates. Since `expand.covs` expects an *msdata* object, we set the class of the *newdata* data to *msdata* explicitly. We also copy the levels of the categorical covariates before expanding, although this is not really necessary here.

```
> newd <- data.frame(dissub = rep(0, 3), age = rep(0, 3), drmatch = rep(0,
+     3), tcd = rep(0, 3), trans = 1:3)
> newd$dissub <- factor(newd$dissub, levels = 0:2, labels = levels(ebmt3$dissub))
> newd$age <- factor(newd$age, levels = 0:2, labels = levels(ebmt3$age))
> newd$drmatch <- factor(newd$drmatch, levels = 0:1, labels = levels(ebmt3$drmatch))
> newd$tcd <- factor(newd$tcd, levels = 0:1, labels = levels(ebmt3$tcd))
```

```
> attr(newd, "trans") <- tmat
> class(newd) <- c("msdata", "data.frame")
> newd <- expand.covs(newd, covs[1:4], longnames = FALSE)
> newd$strata = 1:3
> newd
```

An object of class 'msdata'

Data:
```
  dissub  age              drmatch    tcd trans dissub1.1 dissub1.2 dissub1.3
1    AML <=20 No gender mismatch No TCD     1         0         0         0
2    AML <=20 No gender mismatch No TCD     2         0         0         0
3    AML <=20 No gender mismatch No TCD     3         0         0         0
  dissub2.1 dissub2.2 dissub2.3 age1.1 age1.2 age1.3 age2.1 age2.2 age2.3
1         0         0         0      0      0      0      0      0      0
2         0         0         0      0      0      0      0      0      0
3         0         0         0      0      0      0      0      0      0
  drmatch.1 drmatch.2 drmatch.3 tcd.1 tcd.2 tcd.3 strata
1         0         0         0     0     0     0      1
2         0         0         0     0     0     0      2
3         0         0         0     0     0     0      3
```

The last command where the column **strata** is added is important and points to a second major difference between *survfit* and *msfit*. The *newdata* data frame needs to have a column **strata** specifying to which stratum in the **coxph** object each transition belongs. Here each transition corresponds to a separate stratum, so we specify 1, 2, and 3.

To obtain an estimate of the baseline cumulative hazard for the "stratified hazards" model, *msfit* can be called with the first Cox model, **c1**, as input model, and **newd** as *newdata* argument.

```
> msf1 <- msfit(c1, newdata = newd, trans = tmat)
```

The result is an object of class *msfit*, which is a list with three items, **Haz**, **varHaz**, and **trans**. The item **trans** records the transition matrix used when constructing the *msfit* object. **Haz** contains the estimated cumulative hazard for each of the transitions for the particular patient specified in **newd**, while **varHaz** contains the estimated variances of these cumulative hazards, as well as the covariances for each combination of two transitions. All are evaluated at the time points for which any event in any transition occurs, possibly augmented with the largest (non-event) time point in the data. The *summary* method for *msfit* objects is most conveniently used for a summary. If we also would like to have a look at the covariances, we could set the argument *variance* equal to **TRUE**.

```
> summary(msf1)
```

Transition 1 (head and tail):
```
          time          Haz         seHaz         lower          upper
1 0.002737851 0.0005277714 0.0005290102 7.400248e-05 0.003763964
2 0.008213552 0.0010560892 0.0007502708 2.624139e-04 0.004250249
3 0.010951403 0.0010560892 0.0007502708 2.624139e-04 0.004250249
4 0.016427105 0.0010560892 0.0007502708 2.624139e-04 0.004250249
5 0.019164956 0.0015857558 0.0009219748 5.073865e-04 0.004956027
```

```
6 0.021902806 0.0015857558 0.0009219748 5.073865e-04 0.004956027
```

```
...
        time       Haz      seHaz    lower    upper
500 6.253251 0.9513165 0.07182285 0.8204662 1.103035
501 6.357290 0.9513165 0.07182285 0.8204662 1.103035
502 6.362765 0.9513165 0.07182285 0.8204662 1.103035
503 6.798084 0.9513165 0.07182285 0.8204662 1.103035
504 7.110198 0.9513165 0.07182285 0.8204662 1.103035
505 7.731691 0.9513165 0.07182285 0.8204662 1.103035
```

```
Transition 2 (head and tail):
           time         Haz        seHaz       lower       upper
506 0.002737851 0.0003046955 0.0003077143 4.209506e-05 0.002205469
507 0.008213552 0.0003046955 0.0003077143 4.209506e-05 0.002205469
508 0.010951403 0.0006097444 0.0004396591 1.483833e-04 0.002505594
509 0.016427105 0.0012203981 0.0006340496 4.408243e-04 0.003378606
510 0.019164956 0.0018316171 0.0007912068 7.854882e-04 0.004271001
511 0.021902806 0.0024438486 0.0009303805 1.158829e-03 0.005153820
```

```
...
         time       Haz      seHaz     lower     upper
1005 6.253251 0.5020560 0.08219369 0.3642490 0.6919997
1006 6.357290 0.5020560 0.08219369 0.3642490 0.6919997
1007 6.362765 0.5248419 0.08821373 0.3775385 0.7296182
1008 6.798084 0.5248419 0.08821373 0.3775385 0.7296182
1009 7.110198 0.5248419 0.08821373 0.3775385 0.7296182
1010 7.731691 0.5248419 0.08821373 0.3775385 0.7296182
```

```
Transition 3 (head and tail):
            time Haz seHaz lower upper
1011 0.002737851   0     0     0     0
1012 0.008213552   0     0     0     0
1013 0.010951403   0     0     0     0
1014 0.016427105   0     0     0     0
1015 0.019164956   0     0     0     0
1016 0.021902806   0     0     0     0
```

```
...
         time       Haz      seHaz     lower     upper
1510 6.253251 0.3291154 0.05058502 0.2435110 0.4448133
1511 6.357290 0.3427115 0.05413323 0.2514645 0.4670688
1512 6.362765 0.3427115 0.05413323 0.2514645 0.4670688
1513 6.798084 0.3693677 0.06340696 0.2638388 0.5171055
1514 7.110198 0.4647197 0.12159613 0.2782724 0.7760899
1515 7.731691 0.4647197 0.12159613 0.2782724 0.7760899
```

Let us have a closer look at some of the variances and covariances as well.

```
> vH1 <- msf1$varHaz
```

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```
> head(vH1[vH1$trans1 == 1 & vH1$trans2 == 1, ])

          time         varHaz trans1 trans2
1 0.002737851 2.798518e-07      1      1
2 0.008213552 5.629062e-07      1      1
3 0.010951403 5.629062e-07      1      1
4 0.016427105 5.629062e-07      1      1
5 0.019164956 8.500376e-07      1      1
6 0.021902806 8.500376e-07      1      1


> tail(vH1[vH1$trans1 == 1 & vH1$trans2 == 1, ])

        time         varHaz trans1 trans2
500 6.253251 0.005158522      1      1
501 6.357290 0.005158522      1      1
502 6.362765 0.005158522      1      1
503 6.798084 0.005158522      1      1
504 7.110198 0.005158522      1      1
505 7.731691 0.005158522      1      1


> tail(vH1[vH1$trans1 == 1 & vH1$trans2 == 2, ])

         time         varHaz trans1 trans2
1005 6.253251 4.619269e-20      1      2
1006 6.357290 4.619269e-20      1      2
1007 6.362765 4.831165e-20      1      2
1008 6.798084 4.831165e-20      1      2
1009 7.110198 4.831165e-20      1      2
1010 7.731691 4.831165e-20      1      2


> tail(vH1[vH1$trans1 == 1 & vH1$trans2 == 3, ])

         time          varHaz trans1 trans2
1510 6.253251 -2.519108e-21      1      3
1511 6.357290 -2.596219e-21      1      3
1512 6.362765 -2.596219e-21      1      3
1513 6.798084 -2.678371e-21      1      3
1514 7.110198 -2.993363e-21      1      3
1515 7.731691 -2.993363e-21      1      3


> tail(vH1[vH1$trans1 == 2 & vH1$trans2 == 3, ])

         time          varHaz trans1 trans2
2520 6.253251 -3.961164e-38      2      3
2521 6.357290 -4.082418e-38      2      3
2522 6.362765 -4.269688e-38      2      3
2523 6.798084 -4.404793e-38      2      3
2524 7.110198 -4.922821e-38      2      3
2525 7.731691 -4.922821e-38      2      3
```

Note that the covariances of the estimated cumulative hazards are practically (apart from rounding errors) 0. Theoretically, they should be 0, because with separate strata and separate covariate effects for the different transitions, the estimates of the three transitions could in fact have been estimated as three separate Cox models (this would give exactly the same results).

The estimated baseline cumulative hazards for the Markov PH model are obtained in mostly the same way. The only exception is the specification of the *strata* argument in `newd`. Instead of taking the values 1, 2, and 3, for the three transitions, they take values 1, 2, 2, to indicate that transition 1 corresponds to stratum 1, and both transitions 2 and 3 correspond to stratum 2 (the order of the strata as defined in the `coxph` object). Also the time-dependent covariate `pr` needs to be included, taking the value 0 for transitions 1 and 2, and 1 for transition 3.

```
> newd$strata = c(1, 2, 2)
> newd$pr <- c(0, 0, 1)
> msf2 <- msfit(c2, newdata = newd, trans = tmat)
> summary(msf2)

Transition 1 (head and tail):
          time           Haz          seHaz          lower        upper
1 0.002737851 0.0005277714 0.0005290102 7.400248e-05 0.003763964
2 0.008213552 0.0010560892 0.0007502708 2.624139e-04 0.004250249
3 0.010951403 0.0010560892 0.0007502708 2.624139e-04 0.004250249
4 0.016427105 0.0010560892 0.0007502708 2.624139e-04 0.004250249
5 0.019164956 0.0015857558 0.0009219748 5.073865e-04 0.004956027
6 0.021902806 0.0015857558 0.0009219748 5.073865e-04 0.004956027


...
        time       Haz      seHaz     lower     upper
500 6.253251 0.9513165 0.07182285 0.8204662 1.103035
501 6.357290 0.9513165 0.07182285 0.8204662 1.103035
502 6.362765 0.9513165 0.07182285 0.8204662 1.103035
503 6.798084 0.9513165 0.07182285 0.8204662 1.103035
504 7.110198 0.9513165 0.07182285 0.8204662 1.103035
505 7.731691 0.9513165 0.07182285 0.8204662 1.103035


Transition 2 (head and tail):
            time          Haz         seHaz        lower        upper
506 0.002737851 0.0003053084 0.0003083331 4.217979e-05 0.002209902
507 0.008213552 0.0003053084 0.0003083331 4.217979e-05 0.002209902
508 0.010951403 0.0006107971 0.0004404176 1.486397e-04 0.002509915
509 0.016427105 0.0012223306 0.0006350522 4.415233e-04 0.003383948
510 0.019164956 0.0018344413 0.0007924245 7.867013e-04 0.004277576
511 0.021902806 0.0024473467 0.0009317088 1.160491e-03 0.005161183


...
         time       Haz      seHaz     lower     upper
1005 6.253251 0.5040408 0.07806657 0.3720749 0.6828118
1006 6.357290 0.5146993 0.08030652 0.3790914 0.6988167
1007 6.362765 0.5255361 0.08256535 0.3862540 0.7150431
1008 6.798084 0.5476683 0.08851937 0.3989682 0.7517906
1009 7.110198 0.6357669 0.13427464 0.4202651 0.9617730
```

```
1010 7.731691 0.6357669 0.13427464 0.4202651 0.9617730


Transition 3 (head and tail):
             time          Haz         seHaz        lower       upper
1011 0.002737851 0.0002090742 0.0002116301 2.875366e-05 0.001520225
1012 0.008213552 0.0002090742 0.0002116301 2.875366e-05 0.001520225
1013 0.010951403 0.0004182719 0.0003029499 1.011445e-04 0.001729717
1014 0.016427105 0.0008370481 0.0004386272 2.997137e-04 0.002337729
1015 0.019164956 0.0012562195 0.0005493845 5.330994e-04 0.002960212
1016 0.021902806 0.0016759351 0.0006481990 7.853066e-04 0.003576640


...
         time          Haz        seHaz       lower      upper
1510 6.253251 0.3451655 0.05260815 0.2560308 0.4653317
1511 6.357290 0.3524644 0.05411648 0.2608699 0.4762189
1512 6.362765 0.3598855 0.05563688 0.2658103 0.4872555
1513 6.798084 0.3750415 0.05964162 0.2746095 0.5122042
1514 7.110198 0.4353712 0.09072076 0.2893943 0.6549820
1515 7.731691 0.4353712 0.09072076 0.2893943 0.6549820

> vH2 <- msf2$varHaz
> tail(vH2[vH2$trans1 == 1 & vH2$trans2 == 2, ])

         time           varHaz trans1 trans2
1005 6.253251 -3.271456e-20      1      2
1006 6.357290 -3.340788e-20      1      2
1007 6.362765 -3.411206e-20      1      2
1008 6.798084 -3.558751e-20      1      2
1009 7.110198 -4.217008e-20      1      2
1010 7.731691 -4.217008e-20      1      2

> tail(vH2[vH2$trans1 == 1 & vH2$trans2 == 3, ])

         time           varHaz trans1 trans2
1510 6.253251 2.603403e-20      1      3
1511 6.357290 2.658350e-20      1      3
1512 6.362765 2.714266e-20      1      3
1513 6.798084 2.825912e-20      1      3
1514 7.110198 3.221742e-20      1      3
1515 7.731691 3.221742e-20      1      3

> tail(vH2[vH2$trans1 == 2 & vH2$trans2 == 3, ])

         time           varHaz trans1 trans2
2520 6.253251 0.0004142378      2      3
2521 6.357290 0.0005227029      2      3
2522 6.362765 0.0006348311      2      3
2523 6.798084 0.0011112104      2      3
2524 7.110198 0.0088628795      2      3
2525 7.731691 0.0088628795      2      3
```

Note that the estimated cumulative hazards and variances for transition 1 are identical to those from `msf1`. We saw earlier that the estimated regression coefficients were also identical for the Markov stratified and the Markon PH models. Note also that the variance of the cumulative hazard of transition 3 (and 2, not shown) is smaller than with `msf1`. The cumulative hazard estimates of transitions 1 and 2 are still uncorrelated (and 1 and 3), but those of transitions 2 and 3 are correlated now, because they share a common baseline.

Let us compare the baseline hazards of the Markov stratified and PH models graphically. For this we use the `plot` method for *msfit* objects. Figure 1 corresponds to Figure 14 in the tutorial.

```
> par(mfrow = c(1, 2))
> plot(msf1, cols = rep(1, 3), lwd = 2, lty = 1:3, xlab = "Years since transplant",
+     ylab = "Stratified baseline hazards", legend.pos = c(2, 0.9))
> plot(msf2, cols = rep(1, 3), lwd = 2, lty = 1:3, xlab = "Years since transplant",
+     ylab = "Proportional baseline hazards", legend.pos = c(2,
+         0.9))
> par(mfrow = c(1, 1))
```
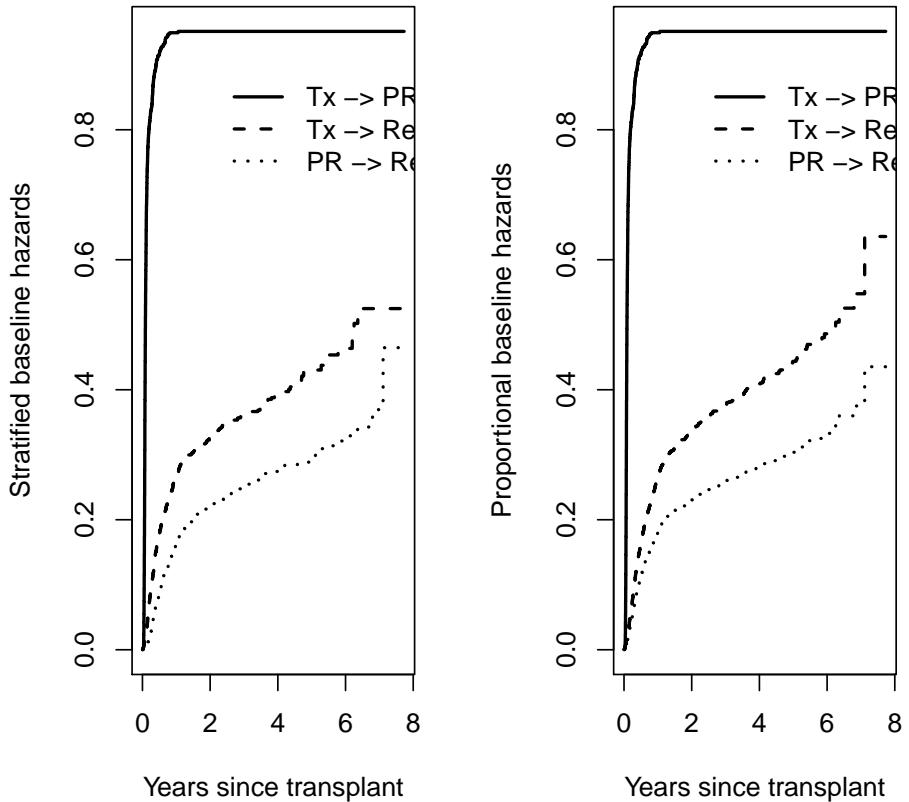

Figure 1: Baseline cumulative hazard curves for the EBMT illness-death model. On the left the Markov stratified hazards model, on the right the Markov PH model.

Define the multi-state model as $X(t)$, a random process taking values in $1, \ldots, S$ (S being the

number of states). We are interested in estimating so called transition probabilities $P_{gh}(s,t) = P(X(t) = h \mid X(s) = g)$, possibly depending on covariates. For instance, $P_{13}(0,t)$ indicates the probability of having relapsed/died (state 3) by time t, given that the individual was alive without relapse or platelet recovery (state 1) at time $s = 0$. By fixing s and varying t, we can predict the future behavior of the multi-state model given the present at time s. For Markov models, these probabilities will depend only on the state at time s, not on what happened before. For these Markov models there is a powerful relation between these transition probabilities and the transition intensities, given by

$$(1) \qquad \mathbf{P}(s,t) = \prod_{(s,t]} (\mathbf{I} + d\mathbf{\Lambda}(u))$$

Here $\mathbf{P}(s,t)$ is an $S \times S$ matrix with as (g,h) element the $P_{gh}(s,t)$ in which we are interested, and $\mathbf{\Lambda}(t)$ is an $S \times S$ matrix with as off-diagonal (g,h) elements the transition intensities $\Lambda_{gh}(t)$ of transition $g \to h$. If such a direct transition is not possible, then $\Lambda_{gh}(t) = 0$. The diagonal elements of $\mathbf{\Lambda}(t)$ are defined as $\Lambda_{gg}(t) = -\sum_{h \neq g} \Lambda_{gh}(t)$, i.e. as minus the sum of the transition intensities of the transitions out from state g. Finally, $\mathbf{I}$ is the $S \times S$ identity matrix. Equation (1) describes a theoretical relation between the true underlying transition intensities and transition probabilities. The product is a so called product integral (Andersen et al. 1993) when the transition intensities are continuous.

We already have estimates of all the transition intensities. If we gather these in a matrix and plug them in equation (1), we get

$$(2) \qquad \hat{\mathbf{P}}(s,t) = \prod_{s < u \leq t} \left(\mathbf{I} + d\hat{\mathbf{\Lambda}}(u) \right)$$

as an estimate of the transition probabilities. This estimator is called the Aalen-Johansen estimator, and it is implemented in *probtrans*. By working with matrices, we immediately get all the transition probabilities from all the starting states g to all the receiving states h in one go. When we fix s, we can calculate all these transition probabilities by forward matrix multiplications using the simple recursive relation

$$\hat{\mathbf{P}}(s,t+) = \hat{\mathbf{P}}(s,t) \cdot \left(\mathbf{I} + d\hat{\mathbf{\Lambda}}(t+) \right) \ .$$

Andersen et al. (1993) and de Wreede et al. (2009) also describe recursive formulas for the covariance matrix of $\hat{\mathbf{P}}(s,t)$, with and without covariates, which are implemented in *mstate*.

Let us see all this theory in action and let us recreate Figure 15 of the tutorial. For this we need to calculate transition probabilities for a baseline patient, based on the Markov PH model. We thus use `msf2` as input for *probtrans*. By default, *probtrans* uses forward prediction, which means that s is kept fixed and $t > s$. The argument *predt* specifies either s or t. In this case (forward prediction) it specifies s. From version 0.2.3 on, *probtrans* no longer needs a *trans* argument, but takes that from the `trans` item of the *msfit* object.

```
> pt <- probtrans(msf2, predt = 0)
```

The result of *probtrans* is a *probtrans* object, which is a list, where item [[i]] contains predictions from state i. Each item of the list is a data frame with `time` containing all event time points, and `pstate1`, `pstate2`, etc the probabilities of being in state 1, 2, etc, and finally `se1`, `se2` etc the standard errors of these estimated probabilities. The item [[3]] contains predictions $\hat{P}_{3h}(0,t)$ (we chose $s = 0$) starting from the RelDeath state, which is absorbing.

```
> head(pt[[3]])
```

```
        time pstate1 pstate2 pstate3 se1 se2 se3
1 0.000000000       0       0       1   0   0   0
2 0.002737851       0       0       1   0   0   0
3 0.008213552       0       0       1   0   0   0
4 0.010951403       0       0       1   0   0   0
5 0.016427105       0       0       1   0   0   0
6 0.019164956       0       0       1   0   0   0
```

> *tail(pt[[3]])*

```
        time pstate1 pstate2 pstate3 se1 se2 se3
501 6.253251       0       0       1   0   0   0
502 6.357290       0       0       1   0   0   0
503 6.362765       0       0       1   0   0   0
504 6.798084       0       0       1   0   0   0
505 7.110198       0       0       1   0   0   0
506 7.731691       0       0       1   0   0   0
```

We see that these prediction probabilities are not so interesting; the probabilities are all 0 or 1, and, since there is no randomness, all the SE's are 0. Item `[[2]]` contains predictions $\hat{P}_{2h}(0, t)$ from state 2.

It is easier to use the **summary** method for *probtrans* objects. The user may specify a *from* argument, specifying from which state the predictions are to be printed. The **summary** method prints a selection, the **head** and **tail** by default unless there are fewer than 12 time points. When *complete* is set to TRUE, predictions for all time points are printed. If the *from* argument is missing in the function call, then predictions from all states are printed.

> *summary(pt, from = 2)*

```
Prediction from state 2 :
          time pstate1   pstate2       pstate3 se1        se2           se3
1    0.000000000       0 1.0000000 0.0000000000   0 0.0000000000 0.0000000000
2    0.002737851       0 0.9997909 0.0002090742   0 0.0002115858 0.0002115858
3    0.008213552       0 0.9997909 0.0002090742   0 0.0002115858 0.0002115858
4    0.010951403       0 0.9995818 0.0004182281   0 0.0003028232 0.0003028232
5    0.016427105       0 0.9991632 0.0008368292   0 0.0004382601 0.0004382601
6    0.019164956       0 0.9987444 0.0012556499   0 0.0005486946 0.0005486946
7    0.021902806       0 0.9983252 0.0016748385   0 0.0006471134 0.0006471134
8    0.024640657       0 0.9979058 0.0020941700   0 0.0007382674 0.0007382674
9    0.027378508       0 0.9979058 0.0020941700   0 0.0007382674 0.0007382674
10   0.030116359       0 0.9976960 0.0023039813   0 0.0007819551 0.0007819551
11   0.032854209       0 0.9966467 0.0033533327   0 0.0009875792 0.0009875792
12   0.035592060       0 0.9964364 0.0035635857   0 0.0010269915 0.0010269915
13   0.038329911       0 0.9951731 0.0048268856   0 0.0012554415 0.0012554415
14   0.041067762       0 0.9947501 0.0052499465   0 0.0013296997 0.0013296997
15   0.043805613       0 0.9947501 0.0052499465   0 0.0013296997 0.0013296997
16   0.046543463       0 0.9945366 0.0054633694   0 0.0013668758 0.0013668758
17   0.049281314       0 0.9943219 0.0056780509   0 0.0014040833 0.0014040833
18   0.052019165       0 0.9938905 0.0061095068   0 0.0014782696 0.0014782696
19   0.054757016       0 0.9936735 0.0063265199   0 0.0015153446 0.0015153446
```

20	0.057494867	0	0.9925813	0.0074187085	0	0.0016993040	0.0016993040
21	0.060232717	0	0.9921418	0.0078582244	0	0.0017723751	0.0017723751
22	0.062970568	0	0.9919205	0.0080795369	0	0.0018089881	0.0018089881
23	0.065708419	0	0.9916974	0.0083025976	0	0.0018457649	0.0018457649
24	0.068446270	0	0.9910234	0.0089765698	0	0.0019560576	0.0019560576
25	0.071184120	0	0.9907973	0.0092026909	0	0.0019928405	0.0019928405
26	0.073921971	0	0.9907973	0.0092026909	0	0.0019928405	0.0019928405
27	0.076659822	0	0.9901081	0.0098918633	0	0.0021043311	0.0021043311
28	0.079397673	0	0.9896456	0.0103544261	0	0.0021786853	0.0021786853
29	0.082135524	0	0.9882481	0.0117519281	0	0.0024008188	0.0024008188
30	0.084873374	0	0.9875448	0.0124551726	0	0.0025115528	0.0025115528
31	0.087611225	0	0.9870736	0.0129264204	0	0.0025853005	0.0025853005
32	0.090349076	0	0.9868370	0.0131630100	0	0.0026222339	0.0026222339
33	0.093086927	0	0.9865994	0.0134005604	0	0.0026592330	0.0026592330
34	0.095824778	0	0.9851694	0.0148306199	0	0.0028803426	0.0028803426
35	0.098562628	0	0.9851694	0.0148306199	0	0.0028803426	0.0028803426
36	0.101300479	0	0.9851694	0.0148306199	0	0.0028803426	0.0028803426
37	0.104038330	0	0.9849286	0.0150714175	0	0.0029173767	0.0029173767
38	0.106776181	0	0.9846868	0.0153132001	0	0.0029544905	0.0029544905
39	0.109514031	0	0.9839600	0.0160399907	0	0.0030656314	0.0030656314
40	0.112251882	0	0.9837167	0.0162832522	0	0.0031027188	0.0031027188
41	0.114989733	0	0.9837167	0.0162832522	0	0.0031027188	0.0031027188
42	0.117727584	0	0.9827398	0.0172602467	0	0.0032508677	0.0032508677
43	0.120465435	0	0.9824950	0.0175049699	0	0.0032878625	0.0032878625
44	0.123203285	0	0.9815155	0.0184844739	0	0.0034353951	0.0034353951
45	0.125941136	0	0.9810250	0.0189749929	0	0.0035090190	0.0035090190
46	0.128678987	0	0.9797966	0.0202034490	0	0.0036926352	0.0036926352
47	0.131416838	0	0.9795502	0.0204498364	0	0.0037293440	0.0037293440
48	0.134154689	0	0.9788101	0.0211898906	0	0.0038392369	0.0038392369
49	0.136892539	0	0.9783152	0.0216847801	0	0.0039125482	0.0039125482
50	0.139630390	0	0.9778190	0.0221810154	0	0.0039859200	0.0039859200
51	0.142368241	0	0.9768255	0.0231744814	0	0.0041323397	0.0041323397
52	0.145106092	0	0.9760795	0.0239204727	0	0.0042420002	0.0042420002
53	0.147843943	0	0.9748347	0.0251652806	0	0.0044243187	0.0044243187
54	0.150581793	0	0.9745850	0.0254149736	0	0.0044608200	0.0044608200
55	0.153319644	0	0.9735852	0.0264147803	0	0.0046065343	0.0046065343
56	0.156057495	0	0.9720825	0.0279175354	0	0.0048247143	0.0048247143
57	0.158795346	0	0.9713282	0.0286718152	0	0.0049339122	0.0049339122
58	0.161533196	0	0.9703215	0.0296785269	0	0.0050792896	0.0050792896
59	0.164271047	0	0.9693137	0.0306862643	0	0.0052245305	0.0052245305
60	0.167008898	0	0.9688092	0.0311908223	0	0.0052971486	0.0052971486
61	0.169746749	0	0.9683037	0.0316962510	0	0.0053698084	0.0053698084
62	0.172484600	0	0.9680508	0.0319491720	0	0.0054061539	0.0054061539
63	0.175222450	0	0.9670384	0.0329616059	0	0.0055513759	0.0055513759
64	0.177960301	0	0.9662780	0.0337220422	0	0.0056602721	0.0056602721
65	0.180698152	0	0.9657701	0.0342298951	0	0.0057329001	0.0057329001
66	0.183436003	0	0.9652618	0.0347381659	0	0.0058054936	0.0058054936
67	0.186173854	0	0.9639888	0.0360112363	0	0.0059869295	0.0059869295
68	0.188911704	0	0.9637336	0.0362664430	0	0.0060232687	0.0060232687

69	0.191649555	0	0.9634781	0.0365218674	0	0.0060596170	0.0060596170
70	0.194387406	0	0.9609225	0.0390775020	0	0.0064217447	0.0064217447
71	0.197125257	0	0.9601539	0.0398460910	0	0.0065303961	0.0065303961
72	0.199863107	0	0.9601539	0.0398460910	0	0.0065303961	0.0065303961
73	0.202600958	0	0.9591272	0.0408728032	0	0.0066752892	0.0066752892
74	0.205338809	0	0.9588700	0.0411299702	0	0.0067115588	0.0067115588
75	0.208076660	0	0.9580977	0.0419023219	0	0.0068203342	0.0068203342
76	0.210814511	0	0.9580977	0.0419023219	0	0.0068203342	0.0068203342
77	0.213552361	0	0.9573242	0.0426758306	0	0.0069290903	0.0069290903
78	0.216290212	0	0.9560317	0.0439682788	0	0.0071104634	0.0071104634
79	0.219028063	0	0.9557726	0.0442273885	0	0.0071467986	0.0071467986
80	0.221765914	0	0.9552540	0.0447459593	0	0.0072194379	0.0072194379
81	0.224503765	0	0.9544755	0.0455244976	0	0.0073283583	0.0073283583
82	0.227241615	0	0.9544755	0.0455244976	0	0.0073283583	0.0073283583
83	0.229979466	0	0.9534353	0.0465646989	0	0.0074736132	0.0074736132
84	0.232717317	0	0.9529147	0.0470853054	0	0.0075462452	0.0075462452
85	0.235455168	0	0.9526540	0.0473459855	0	0.0075826079	0.0075826079
86	0.238193018	0	0.9510878	0.0489122349	0	0.0078005284	0.0078005284
87	0.243668720	0	0.9495168	0.0504832218	0	0.0080185257	0.0080185257
88	0.246406571	0	0.9489922	0.0510078030	0	0.0080912638	0.0080912638
89	0.249144422	0	0.9484673	0.0515326757	0	0.0081639909	0.0081639909
90	0.251882272	0	0.9479417	0.0520583230	0	0.0082367933	0.0082367933
91	0.254620123	0	0.9474155	0.0525845408	0	0.0083096441	0.0083096441
92	0.257357974	0	0.9463626	0.0536373633	0	0.0084551519	0.0084551519
93	0.260095825	0	0.9455718	0.0544282418	0	0.0085643206	0.0085643206
94	0.262833676	0	0.9453078	0.0546922419	0	0.0086007505	0.0086007505
95	0.265571526	0	0.9445154	0.0554846323	0	0.0087099674	0.0087099674
96	0.268309377	0	0.9437223	0.0562776516	0	0.0088190979	0.0088190979
97	0.271047228	0	0.9423988	0.0576012113	0	0.0090009133	0.0090009133
98	0.273785079	0	0.9423988	0.0576012113	0	0.0090009133	0.0090009133
99	0.276522930	0	0.9416022	0.0583978478	0	0.0091101808	0.0091101808
100	0.279260780	0	0.9405396	0.0594604433	0	0.0092557441	0.0092557441
101	0.281998631	0	0.9402735	0.0597264915	0	0.0092921719	0.0092921719
102	0.284736482	0	0.9394744	0.0605255740	0	0.0094015161	0.0094015161
103	0.287474333	0	0.9386736	0.0613263646	0	0.0095109448	0.0095109448
104	0.290212183	0	0.9378714	0.0621285857	0	0.0096204190	0.0096204190
105	0.292950034	0	0.9373359	0.0626641040	0	0.0096934026	0.0096934026
106	0.295687885	0	0.9367997	0.0632002787	0	0.0097663746	0.0097663746
107	0.298425736	0	0.9357258	0.0642742334	0	0.0099123218	0.0099123218
108	0.301163587	0	0.9357258	0.0642742334	0	0.0099123218	0.0099123218
109	0.303901437	0	0.9343814	0.0656186158	0	0.0100946478	0.0100946478
110	0.306639288	0	0.9335736	0.0664264022	0	0.0102040524	0.0102040524
111	0.309377139	0	0.9327638	0.0672361757	0	0.0103136406	0.0103136406
112	0.312114990	0	0.9322234	0.0677765957	0	0.0103867089	0.0103867089
113	0.314852841	0	0.9314120	0.0685879956	0	0.0104962783	0.0104962783
114	0.317590691	0	0.9305994	0.0694005733	0	0.0106058848	0.0106058848
115	0.320328542	0	0.9297867	0.0702133289	0	0.0107154131	0.0107154131
116	0.323066393	0	0.9289725	0.0710274910	0	0.0108250407	0.0108250407
117	0.325804244	0	0.9276143	0.0723856612	0	0.0110075784	0.0110075784

118	0.328542094	0	0.9273423	0.0726576660	0	0.0110441415	0.0110441415
119	0.331279945	0	0.9267979	0.0732020747	0	0.0111172692	0.0111172692
120	0.334017796	0	0.9262528	0.0737471727	0	0.0111904296	0.0111904296
121	0.336755647	0	0.9246158	0.0753842216	0	0.0114096431	0.0114096431
122	0.339493498	0	0.9240694	0.0759305694	0	0.0114827458	0.0114827458
123	0.342231348	0	0.9229754	0.0770245945	0	0.0116289060	0.0116289060
124	0.344969199	0	0.9224276	0.0775724022	0	0.0117020289	0.0117020289
125	0.347707050	0	0.9216053	0.0783947326	0	0.0118116820	0.0118116820
126	0.353182752	0	0.9210559	0.0789440600	0	0.0118848941	0.0118848941
127	0.355920602	0	0.9207808	0.0792191515	0	0.0119215345	0.0119215345
128	0.361396304	0	0.9196785	0.0803215038	0	0.0120681109	0.0120681109
129	0.364134155	0	0.9185734	0.0814266026	0	0.0122148240	0.0122148240
130	0.366872005	0	0.9180201	0.0819798949	0	0.0122882164	0.0122882164
131	0.369609856	0	0.9174663	0.0825336692	0	0.0123616235	0.0123616235
132	0.372347707	0	0.9171892	0.0828107850	0	0.0123983419	0.0123983419
133	0.375085558	0	0.9166348	0.0833652296	0	0.0124717485	0.0124717485
134	0.377823409	0	0.9155253	0.0844747209	0	0.0126184156	0.0126184156
135	0.380561259	0	0.9138584	0.0861415776	0	0.0128382516	0.0128382516
136	0.383299110	0	0.9133019	0.0866981050	0	0.0129115890	0.0129115890
137	0.386036961	0	0.9121872	0.0878128429	0	0.0130582546	0.0130582546
138	0.388774812	0	0.9116290	0.0883710059	0	0.0131316259	0.0131316259
139	0.394250513	0	0.9110703	0.0889296503	0	0.0132049857	0.0132049857
140	0.396988364	0	0.9110703	0.0889296503	0	0.0132049857	0.0132049857
141	0.399726215	0	0.9110703	0.0889296503	0	0.0132049857	0.0132049857
142	0.405201916	0	0.9105105	0.0894895420	0	0.0132784384	0.0132784384
143	0.407939767	0	0.9102298	0.0897701517	0	0.0133152462	0.0133152462
144	0.410677618	0	0.9096685	0.0903315227	0	0.0133888232	0.0133888232
145	0.413415469	0	0.9088258	0.0911741838	0	0.0134991204	0.0134991204
146	0.416153320	0	0.9088258	0.0911741838	0	0.0134991204	0.0134991204
147	0.418891170	0	0.9079815	0.0920184741	0	0.0136095094	0.0136095094
148	0.421629021	0	0.9071358	0.0928641732	0	0.0137199468	0.0137199468
149	0.424366872	0	0.9062892	0.0937108019	0	0.0138303836	0.0138303836
150	0.427104723	0	0.9057241	0.0942758522	0	0.0139040401	0.0139040401
151	0.432580424	0	0.9048757	0.0951243062	0	0.0140145438	0.0140145438
152	0.435318275	0	0.9043095	0.0956904633	0	0.0140882101	0.0140882101
153	0.438056126	0	0.9040262	0.0959738025	0	0.0141250740	0.0141250740
154	0.440793977	0	0.9031756	0.0968244431	0	0.0142356150	0.0142356150
155	0.443531828	0	0.9031756	0.0968244431	0	0.0142356150	0.0142356150
156	0.446269678	0	0.9031756	0.0968244431	0	0.0142356150	0.0142356150
157	0.449007529	0	0.9026077	0.0973923346	0	0.0143093585	0.0143093585
158	0.451745380	0	0.9020391	0.0979609087	0	0.0143831280	0.0143831280
159	0.454483231	0	0.9014701	0.0985298976	0	0.0144568892	0.0144568892
160	0.457221081	0	0.9011854	0.0988146096	0	0.0144937872	0.0144937872
161	0.459958932	0	0.9003310	0.0996689842	0	0.0146043798	0.0146043798
162	0.465434634	0	0.8991904	0.1008095902	0	0.0147518995	0.0147518995
163	0.470910335	0	0.8989049	0.1010950968	0	0.0147888077	0.0147888077
164	0.473648186	0	0.8983336	0.1016664408	0	0.0148626207	0.0148626207
165	0.476386037	0	0.8977618	0.1022382256	0	0.0149364268	0.0149364268
166	0.479123888	0	0.8974756	0.1025243630	0	0.0149733593	0.0149733593

167	0.481861739	0	0.8971894	0.1028105690	0	0.0150102851	0.0150102851
168	0.484599589	0	0.8963305	0.1036694826	0	0.0151209708	0.0151209708
169	0.487337440	0	0.8957573	0.1042426559	0	0.0151947629	0.0151947629
170	0.492813142	0	0.8951836	0.1048164329	0	0.0152685715	0.0152685715
171	0.495550992	0	0.8948965	0.1051035206	0	0.0153054898	0.0153054898
172	0.498288843	0	0.8943213	0.1056786939	0	0.0153793953	0.0153793953
173	0.501026694	0	0.8934576	0.1065423515	0	0.0154902019	0.0154902019
174	0.503764545	0	0.8928811	0.1071188697	0	0.0155641120	0.0155641120
175	0.506502396	0	0.8925927	0.1074072995	0	0.0156010788	0.0156010788
176	0.509240246	0	0.8925927	0.1074072995	0	0.0156010788	0.0156010788
177	0.511978097	0	0.8911482	0.1088518115	0	0.0157858458	0.0157858458
178	0.514715948	0	0.8902805	0.1097195144	0	0.0158966885	0.0158966885
179	0.517453799	0	0.8899909	0.1100090732	0	0.0159336600	0.0159336600
180	0.520191650	0	0.8899909	0.1100090732	0	0.0159336600	0.0159336600
181	0.522929500	0	0.8894110	0.1105889641	0	0.0160076228	0.0160076228
182	0.528405202	0	0.8891208	0.1108791858	0	0.0160446291	0.0160446291
183	0.531143053	0	0.8885403	0.1114596769	0	0.0161185887	0.0161185887
184	0.533880903	0	0.8876686	0.1123314248	0	0.0162294864	0.0162294864
185	0.536618754	0	0.8870869	0.1129130610	0	0.0163034057	0.0163034057
186	0.542094456	0	0.8862137	0.1137863194	0	0.0164142445	0.0164142445
187	0.547570157	0	0.8859223	0.1140776720	0	0.0164511984	0.0164511984
188	0.550308008	0	0.8859223	0.1140776720	0	0.0164511984	0.0164511984
189	0.553045859	0	0.8847547	0.1152452801	0	0.0165990442	0.0165990442
190	0.555783710	0	0.8844626	0.1155374250	0	0.0166360117	0.0166360117
191	0.558521561	0	0.8838778	0.1161221637	0	0.0167099480	0.0167099480
192	0.561259411	0	0.8832930	0.1167070443	0	0.0167838110	0.0167838110
193	0.566735113	0	0.8830001	0.1169998674	0	0.0168207706	0.0168207706
194	0.572210815	0	0.8824143	0.1175856605	0	0.0168946566	0.0168946566
195	0.577686516	0	0.8815345	0.1184654531	0	0.0170054620	0.0170054620
196	0.580424367	0	0.8812410	0.1187590223	0	0.0170424238	0.0170424238
197	0.585900068	0	0.8803590	0.1196410416	0	0.0171534257	0.0171534257
198	0.588637919	0	0.8791816	0.1208184027	0	0.0173012832	0.0173012832
199	0.591375770	0	0.8782976	0.1217024173	0	0.0174121379	0.0174121379
200	0.599589322	0	0.8780024	0.1219975728	0	0.0174491265	0.0174491265
201	0.602327173	0	0.8774121	0.1225878949	0	0.0175230490	0.0175230490
202	0.605065024	0	0.8768216	0.1231783964	0	0.0175969463	0.0175969463
203	0.607802875	0	0.8762303	0.1237696871	0	0.0176708684	0.0176708684
204	0.610540726	0	0.8759344	0.1240655643	0	0.0177078464	0.0177078464
205	0.613278576	0	0.8756382	0.1243618263	0	0.0177448638	0.0177448638
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208	0.621492129	0	0.8741545	0.1258455051	0	0.0179299737	0.0179299737
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210	0.626967830	0	0.8729645	0.1270355371	0	0.0180781749	0.0180781749
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212	0.635181383	0	0.8720702	0.1279298191	0	0.0181893867	0.0181893867
213	0.637919233	0	0.8717720	0.1282280273	0	0.0182264585	0.0182264585
214	0.640657084	0	0.8714738	0.1285262414	0	0.0182635183	0.0182635183
215	0.643394935	0	0.8711754	0.1288246403	0	0.0183005880	0.0183005880

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229	0.698151951	0	0.8657584	0.1342416464	0	0.0189706263	0.0189706263
230	0.703627652	0	0.8654555	0.1345445138	0	0.0190079385	0.0190079385
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114	0	0.9100427	5.143768e-02	0	0.9516205 0.093636414
115	0	0.9090203	5.206139e-02	0	0.9510275 0.094694190
116	0	0.9079963	5.268633e-02	0	0.9504333 0.095753574
117	0	0.9062888	5.372935e-02	0	0.9494416 0.097519953
118	0	0.9059469	5.393824e-02	0	0.9492431 0.097873731
119	0	0.9052626	5.435639e-02	0	0.9488455 0.098581673
120	0	0.9045776	5.477516e-02	0	0.9484474 0.099290360
121	0	0.9025215	5.603358e-02	0	0.9472509 0.101417414
122	0	0.9018355	5.645366e-02	0	0.9468515 0.102127157
123	0	0.9004623	5.729516e-02	0	0.9460514 0.103547800
124	0	0.8997748	5.771663e-02	0	0.9456507 0.104258996
125	0	0.8987431	5.834947e-02	0	0.9450490 0.105326306
126	0	0.8980541	5.877228e-02	0	0.9446470 0.106039191
127	0	0.8977090	5.898404e-02	0	0.9444456 0.106396131
128	0	0.8963270	5.983301e-02	0	0.9436383 0.107825827
129	0	0.8949421	6.068444e-02	0	0.9428287 0.109258507
130	0	0.8942488	6.111083e-02	0	0.9424233 0.109975654
131	0	0.8935551	6.153766e-02	0	0.9420174 0.110693301
132	0	0.8932080	6.175127e-02	0	0.9418143 0.111052383
133	0	0.8925136	6.217876e-02	0	0.9414078 0.111770674
134	0	0.8911247	6.303453e-02	0	0.9405940 0.113207458
135	0	0.8890392	6.432097e-02	0	0.9393706 0.115364727
136	0	0.8883430	6.475058e-02	0	0.9389620 0.116084843
137	0	0.8869492	6.561145e-02	0	0.9381433 0.117526663
138	0	0.8862514	6.604260e-02	0	0.9377333 0.118248436
139	0	0.8855532	6.647424e-02	0	0.9373228 0.118970640
140	0	0.8855532	6.647424e-02	0	0.9373228 0.118970640
141	0	0.8855532	6.647424e-02	0	0.9373228 0.118970640
142	0	0.8848536	6.690694e-02	0	0.9369112 0.119694276
143	0	0.8845030	6.712382e-02	0	0.9367050 0.120056939
144	0	0.8838018	6.755777e-02	0	0.9362923 0.120782312
145	0	0.8827494	6.820939e-02	0	0.9356725 0.121870776
146	0	0.8827494	6.820939e-02	0	0.9356725 0.121870776
147	0	0.8816954	6.886246e-02	0	0.9350513 0.122961039
148	0	0.8806399	6.951682e-02	0	0.9344290 0.124052777
149	0	0.8795835	7.017209e-02	0	0.9338057 0.125145407

150	0	0.8788786	7.060950e-02	0	0.9333897	0.125874516
151	0	0.8778204	7.126644e-02	0	0.9327648	0.126969073
152	0	0.8771145	7.170491e-02	0	0.9323478	0.127699272
153	0	0.8767612	7.192435e-02	0	0.9321391	0.128064701
154	0	0.8757008	7.258336e-02	0	0.9315123	0.129161454
155	0	0.8757008	7.258336e-02	0	0.9315123	0.129161454
156	0	0.8757008	7.258336e-02	0	0.9315123	0.129161454
157	0	0.8749931	7.302340e-02	0	0.9310938	0.129893516
158	0	0.8742846	7.346407e-02	0	0.9306746	0.130626300
159	0	0.8735758	7.390515e-02	0	0.9302551	0.131359460
160	0	0.8732212	7.412588e-02	0	0.9300452	0.131726294
161	0	0.8721572	7.478844e-02	0	0.9294150	0.132826766
162	0	0.8707371	7.567316e-02	0	0.9285735	0.134295611
163	0	0.8703817	7.589465e-02	0	0.9283628	0.134663237
164	0	0.8696706	7.633794e-02	0	0.9279412	0.135398797
165	0	0.8689591	7.678167e-02	0	0.9275192	0.136134762
166	0	0.8686030	7.700373e-02	0	0.9273080	0.136503056
167	0	0.8682469	7.722587e-02	0	0.9270967	0.136871400
168	0	0.8671786	7.789271e-02	0	0.9264625	0.137976478
169	0	0.8664658	7.833781e-02	0	0.9260391	0.138713743
170	0	0.8657524	7.878348e-02	0	0.9256152	0.139451630
171	0	0.8653955	7.900649e-02	0	0.9254031	0.139820801
172	0	0.8646806	7.945336e-02	0	0.9249781	0.140560274
173	0	0.8636074	8.012463e-02	0	0.9243396	0.141670212
174	0	0.8628912	8.057280e-02	0	0.9239133	0.142410989
175	0	0.8625330	8.079704e-02	0	0.9237000	0.142781571
176	0	0.8625330	8.079704e-02	0	0.9237000	0.142781571
177	0	0.8607394	8.192061e-02	0	0.9226312	0.144636575
178	0	0.8596624	8.259575e-02	0	0.9219890	0.145750493
179	0	0.8593031	8.282108e-02	0	0.9217747	0.146122172
180	0	0.8593031	8.282108e-02	0	0.9217747	0.146122172
181	0	0.8585836	8.327245e-02	0	0.9213453	0.146866321
182	0	0.8582235	8.349837e-02	0	0.9211304	0.147238724
183	0	0.8575035	8.395033e-02	0	0.9207005	0.147983443
184	0	0.8564226	8.462932e-02	0	0.9200546	0.149101382
185	0	0.8557015	8.508246e-02	0	0.9196235	0.149847097
186	0	0.8546193	8.576300e-02	0	0.9189761	0.150966338
187	0	0.8542583	8.599010e-02	0	0.9187600	0.151339694
188	0	0.8542583	8.599010e-02	0	0.9187600	0.151339694
189	0	0.8528121	8.690057e-02	0	0.9178938	0.152835300
190	0	0.8524503	8.712841e-02	0	0.9176770	0.153209451
191	0	0.8517263	8.758454e-02	0	0.9172431	0.153958188
192	0	0.8510023	8.804091e-02	0	0.9168088	0.154706874
193	0	0.8506399	8.826943e-02	0	0.9165914	0.155081656
194	0	0.8499150	8.872665e-02	0	0.9161564	0.155831277
195	0	0.8488267	8.941360e-02	0	0.9155027	0.156956707
196	0	0.8484636	8.964283e-02	0	0.9152846	0.157332212
197	0	0.8473727	9.033165e-02	0	0.9146293	0.158460285
198	0	0.8459173	9.125158e-02	0	0.9137539	0.159965295

199	0	0.8448249	9.194256e-02	0	0.9130964	0.161094911
200	0	0.8444603	9.217330e-02	0	0.9128769	0.161472008
201	0	0.8437310	9.263487e-02	0	0.9124377	0.162226076
202	0	0.8430017	9.309666e-02	0	0.9119983	0.162980254
203	0	0.8422716	9.355918e-02	0	0.9115582	0.163735253
204	0	0.8419063	9.379063e-02	0	0.9113379	0.164113019
205	0	0.8415405	9.402241e-02	0	0.9111174	0.164491255
206	0	0.8408088	9.448625e-02	0	0.9106760	0.165247884
207	0	0.8400759	9.495105e-02	0	0.9102338	0.166005727
208	0	0.8397094	9.518354e-02	0	0.9100125	0.166384767
209	0	0.8393426	9.541623e-02	0	0.9097911	0.166764042
210	0	0.8382413	9.611528e-02	0	0.9091259	0.167902835
211	0	0.8375062	9.658214e-02	0	0.9086817	0.168662986
212	0	0.8371385	9.681570e-02	0	0.9084595	0.169043231
213	0	0.8367708	9.704928e-02	0	0.9082372	0.169423477
214	0	0.8364031	9.728289e-02	0	0.9080149	0.169803698
215	0	0.8360352	9.751666e-02	0	0.9077925	0.170184123
216	0	0.8356671	9.775069e-02	0	0.9075698	0.170564840
217	0	0.8352986	9.798495e-02	0	0.9073469	0.170945834
218	0	0.8349294	9.821970e-02	0	0.9071235	0.171327653
219	0	0.8345602	9.845450e-02	0	0.9069001	0.171709466
220	0	0.8341905	9.868963e-02	0	0.9066764	0.172091727
221	0	0.8338205	9.892507e-02	0	0.9064524	0.172474377
222	0	0.8330801	9.939640e-02	0	0.9060039	0.173239993
223	0	0.8327097	9.963220e-02	0	0.9057795	0.173622920
224	0	0.8319675	1.001050e-01	0	0.9053296	0.174390475
225	0	0.8312243	1.005785e-01	0	0.9048790	0.175158904
226	0	0.8308524	1.008155e-01	0	0.9046535	0.175543460
227	0	0.8301086	1.012898e-01	0	0.9042021	0.176312603
228	0	0.8297363	1.015273e-01	0	0.9039762	0.176697594
229	0	0.8293637	1.017649e-01	0	0.9037501	0.177082855
230	0	0.8289911	1.020027e-01	0	0.9035238	0.177468189
231	0	0.8282451	1.024788e-01	0	0.9030707	0.178239542
232	0	0.8278714	1.027174e-01	0	0.9028437	0.178625961
233	0	0.8274977	1.029560e-01	0	0.9026166	0.179012383
234	0	0.8271240	1.031947e-01	0	0.9023895	0.179398824
235	0	0.8267500	1.034336e-01	0	0.9021622	0.179785546
236	0	0.8260011	1.039122e-01	0	0.9017067	0.180559846
237	0	0.8260011	1.039122e-01	0	0.9017067	0.180559846
238	0	0.8252518	1.043913e-01	0	0.9012508	0.181334627
239	0	0.8248769	1.046310e-01	0	0.9010226	0.181722263
240	0	0.8241260	1.051115e-01	0	0.9005654	0.182498716
241	0	0.8229992	1.058330e-01	0	0.8998788	0.183663722
242	0	0.8226234	1.060737e-01	0	0.8996497	0.184052352
243	0	0.8222475	1.063144e-01	0	0.8994206	0.184441008
244	0	0.8218714	1.065554e-01	0	0.8991912	0.184829918
245	0	0.8218714	1.065554e-01	0	0.8991912	0.184829918
246	0	0.8211186	1.070379e-01	0	0.8987320	0.185608256
247	0	0.8207418	1.072795e-01	0	0.8985021	0.185997871

248	0	0.8203646	1.075214e-01	0	0.8982719	0.186387872
249	0	0.8199872	1.077634e-01	0	0.8980416	0.186778080
250	0	0.8196098	1.080055e-01	0	0.8978111	0.187168264
251	0	0.8184778	1.087321e-01	0	0.8971196	0.188338662
252	0	0.8181000	1.089747e-01	0	0.8968888	0.188729284
253	0	0.8177219	1.092175e-01	0	0.8966577	0.189120228
254	0	0.8169654	1.097036e-01	0	0.8961951	0.189902351
255	0	0.8165867	1.099470e-01	0	0.8959634	0.190293959
256	0	0.8158289	1.104341e-01	0	0.8954998	0.191077363
257	0	0.8154497	1.106779e-01	0	0.8952677	0.191469437
258	0	0.8154497	1.106779e-01	0	0.8952677	0.191469437
259	0	0.8150698	1.109222e-01	0	0.8950352	0.191862321
260	0	0.8143096	1.114112e-01	0	0.8945699	0.192648314
261	0	0.8135484	1.119009e-01	0	0.8941039	0.193435304
262	0	0.8120250	1.128819e-01	0	0.8931702	0.195010412
263	0	0.8116439	1.131274e-01	0	0.8929366	0.195404504
264	0	0.8105000	1.138645e-01	0	0.8922351	0.196587183
265	0	0.8101184	1.141106e-01	0	0.8920009	0.196981810
266	0	0.8097366	1.143568e-01	0	0.8917666	0.197376578
267	0	0.8093548	1.146030e-01	0	0.8915323	0.197771342
268	0	0.8089725	1.148496e-01	0	0.8912976	0.198166601
269	0	0.8082064	1.153441e-01	0	0.8908270	0.198958735
270	0	0.8078232	1.155914e-01	0	0.8905916	0.199354901
271	0	0.8074397	1.158390e-01	0	0.8903560	0.199751450
272	0	0.8066726	1.163344e-01	0	0.8898846	0.200544531
273	0	0.8062888	1.165823e-01	0	0.8896487	0.200941359
274	0	0.8055204	1.170789e-01	0	0.8891761	0.201735922
275	0	0.8051353	1.173278e-01	0	0.8889392	0.202134093
276	0	0.8039792	1.180755e-01	0	0.8882276	0.203329419
277	0	0.8028222	1.188242e-01	0	0.8875150	0.204525653
278	0	0.8024364	1.190740e-01	0	0.8872774	0.204924547
279	0	0.8020505	1.193238e-01	0	0.8870396	0.205323585
280	0	0.8016645	1.195738e-01	0	0.8868017	0.205722654
281	0	0.8008923	1.200742e-01	0	0.8863255	0.206521043
282	0	0.7997324	1.208264e-01	0	0.8856095	0.207720246
283	0	0.7993453	1.210774e-01	0	0.8853706	0.208120391
284	0	0.7989579	1.213287e-01	0	0.8851314	0.208520903
285	0	0.7981828	1.218319e-01	0	0.8846525	0.209322261
286	0	0.7977949	1.220837e-01	0	0.8844128	0.209723331
287	0	0.7970191	1.225876e-01	0	0.8839332	0.210525421
288	0	0.7966307	1.228400e-01	0	0.8836930	0.210926949
289	0	0.7954647	1.235981e-01	0	0.8829714	0.212132325
290	0	0.7950757	1.238510e-01	0	0.8827306	0.212534532
291	0	0.7946864	1.241043e-01	0	0.8824896	0.212937032
292	0	0.7939065	1.246117e-01	0	0.8820066	0.213743288
293	0	0.7927356	1.253740e-01	0	0.8812810	0.214953813
294	0	0.7923447	1.256286e-01	0	0.8810386	0.215357957
295	0	0.7919536	1.258834e-01	0	0.8807962	0.215762299
296	0	0.7915616	1.261387e-01	0	0.8805532	0.216167532

297	0	0.7895982	1.274187e-01	0	0.8793348 0.218197434
298	0	0.7884178	1.281885e-01	0	0.8786022 0.219417804
299	0	0.7876296	1.287029e-01	0	0.8781127 0.220232747
300	0	0.7868402	1.292182e-01	0	0.8776223 0.221048868
301	0	0.7864448	1.294765e-01	0	0.8773764 0.221457736
302	0	0.7856538	1.299934e-01	0	0.8768845 0.222275439
303	0	0.7852582	1.302520e-01	0	0.8766383 0.222684484
304	0	0.7844648	1.307708e-01	0	0.8761446 0.223504679
305	0	0.7836701	1.312907e-01	0	0.8756497 0.224326259
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307	0	0.7832721	1.315513e-01	0	0.8754017 0.224737761
308	0	0.7824749	1.320733e-01	0	0.8749048 0.225561882
309	0	0.7816772	1.325960e-01	0	0.8744073 0.226386501
310	0	0.7812780	1.328576e-01	0	0.8741583 0.226799156
311	0	0.7800782	1.336445e-01	0	0.8734091 0.228039523
312	0	0.7796779	1.339071e-01	0	0.8731592 0.228453300
313	0	0.7792772	1.341699e-01	0	0.8729090 0.228867488
314	0	0.7788764	1.344330e-01	0	0.8726586 0.229281838
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316	0	0.7776711	1.352244e-01	0	0.8719053 0.230527877
317	0	0.7772689	1.354885e-01	0	0.8716538 0.230943676
318	0	0.7768642	1.357544e-01	0	0.8714008 0.231361988
319	0	0.7764596	1.360202e-01	0	0.8711477 0.231780269
320	0	0.7760539	1.362869e-01	0	0.8708939 0.232199663
321	0	0.7756482	1.365535e-01	0	0.8706401 0.232619026
322	0	0.7752426	1.368203e-01	0	0.8703862 0.233038357
323	0	0.7748364	1.370874e-01	0	0.8701319 0.233458266
324	0	0.7744298	1.373549e-01	0	0.8698773 0.233878569
325	0	0.7740231	1.376225e-01	0	0.8696225 0.234299067
326	0	0.7736161	1.378904e-01	0	0.8693675 0.234719808
327	0	0.7732084	1.381589e-01	0	0.8691120 0.235141196
328	0	0.7728006	1.384275e-01	0	0.8688563 0.235562797
329	0	0.7723928	1.386962e-01	0	0.8686005 0.235984365
330	0	0.7719849	1.389649e-01	0	0.8683447 0.236406014
331	0	0.7715764	1.392341e-01	0	0.8680884 0.236828287
332	0	0.7711659	1.395048e-01	0	0.8678307 0.237252632
333	0	0.7703446	1.400465e-01	0	0.8673151 0.238101548
334	0	0.7695233	1.405883e-01	0	0.8667993 0.238950520
335	0	0.7691123	1.408595e-01	0	0.8665411 0.239375444
336	0	0.7687011	1.411308e-01	0	0.8662828 0.239800464
337	0	0.7682899	1.414023e-01	0	0.8660244 0.240225521
338	0	0.7678785	1.416740e-01	0	0.8657658 0.240650780
339	0	0.7674669	1.419460e-01	0	0.8655069 0.241076347
340	0	0.7670550	1.422181e-01	0	0.8652478 0.241502083
341	0	0.7666422	1.424910e-01	0	0.8649880 0.241928756
342	0	0.7662290	1.427642e-01	0	0.8647280 0.242355858
343	0	0.7658150	1.430380e-01	0	0.8644673 0.242783820
344	0	0.7654004	1.433122e-01	0	0.8642062 0.243212397
345	0	0.7649857	1.435866e-01	0	0.8639450 0.243641073

346	0	0.7645708	1.438612e-01	0	0.8636836	0.244069954
347	0	0.7641554	1.441362e-01	0	0.8634218	0.244499340
348	0	0.7637396	1.444115e-01	0	0.8631597	0.244929110
349	0	0.7633237	1.446869e-01	0	0.8628975	0.245358979
350	0	0.7629066	1.449633e-01	0	0.8626344	0.245790123
351	0	0.7624893	1.452398e-01	0	0.8623711	0.246221437
352	0	0.7620709	1.455171e-01	0	0.8621071	0.246653868
353	0	0.7616513	1.457954e-01	0	0.8618421	0.247087648
354	0	0.7608104	1.463533e-01	0	0.8613110	0.247956757
355	0	0.7603896	1.466326e-01	0	0.8610451	0.248391701
356	0	0.7599682	1.469123e-01	0	0.8607787	0.248827207
357	0	0.7595460	1.471927e-01	0	0.8605117	0.249263629
358	0	0.7591236	1.474733e-01	0	0.8602446	0.249700154
359	0	0.7587012	1.477539e-01	0	0.8599774	0.250136686
360	0	0.7582783	1.480349e-01	0	0.8597098	0.250573770
361	0	0.7578552	1.483162e-01	0	0.8594420	0.251011071
362	0	0.7574317	1.485978e-01	0	0.8591738	0.251448832
363	0	0.7570081	1.488795e-01	0	0.8589056	0.251886641
364	0	0.7561608	1.494433e-01	0	0.8583688	0.252762349
365	0	0.7557362	1.497259e-01	0	0.8580997	0.253201154
366	0	0.7553113	1.500088e-01	0	0.8578304	0.253640352
367	0	0.7548856	1.502922e-01	0	0.8575604	0.254080308
368	0	0.7544594	1.505761e-01	0	0.8572902	0.254520723
369	0	0.7540327	1.508604e-01	0	0.8570194	0.254961750
370	0	0.7536056	1.511450e-01	0	0.8567484	0.255403165
371	0	0.7527462	1.517181e-01	0	0.8562027	0.256291372
372	0	0.7523159	1.520051e-01	0	0.8559294	0.256736092
373	0	0.7518852	1.522924e-01	0	0.8556558	0.257181147
374	0	0.7514507	1.525823e-01	0	0.8553798	0.257630194
375	0	0.7510159	1.528725e-01	0	0.8551035	0.258079629
376	0	0.7505778	1.531649e-01	0	0.8548250	0.258532384
377	0	0.7501393	1.534577e-01	0	0.8545462	0.258985526
378	0	0.7496993	1.537517e-01	0	0.8542663	0.259440267
379	0	0.7492588	1.540460e-01	0	0.8539860	0.259895551
380	0	0.7488173	1.543411e-01	0	0.8537051	0.260351854
381	0	0.7483753	1.546365e-01	0	0.8534238	0.260808598
382	0	0.7479326	1.549325e-01	0	0.8531419	0.261266169
383	0	0.7470434	1.555272e-01	0	0.8525756	0.262185140
384	0	0.7465985	1.558249e-01	0	0.8522922	0.262644928
385	0	0.7457083	1.564208e-01	0	0.8517247	0.263564871
386	0	0.7452606	1.567207e-01	0	0.8514392	0.264027630
387	0	0.7448101	1.570224e-01	0	0.8511518	0.264493194
388	0	0.7439012	1.576317e-01	0	0.8505716	0.265432472
389	0	0.7429912	1.582420e-01	0	0.8499904	0.266372795
390	0	0.7425349	1.585482e-01	0	0.8496988	0.266844361
391	0	0.7420753	1.588565e-01	0	0.8494053	0.267319410
392	0	0.7416155	1.591649e-01	0	0.8491116	0.267794554
393	0	0.7411518	1.594760e-01	0	0.8488154	0.268273816
394	0	0.7406877	1.597874e-01	0	0.8485189	0.268753454

395	0	0.7402221	1.600999e-01	0	0.8482214 0.269234689
396	0	0.7397558	1.604131e-01	0	0.8479232 0.269716690
397	0	0.7392877	1.607275e-01	0	0.8476238 0.270200423
398	0	0.7388194	1.610422e-01	0	0.8473241 0.270684426
399	0	0.7383483	1.613588e-01	0	0.8470227 0.271171304
400	0	0.7378758	1.616763e-01	0	0.8467204 0.271659623
401	0	0.7374032	1.619940e-01	0	0.8464179 0.272148072
402	0	0.7369285	1.623133e-01	0	0.8461139 0.272638701
403	0	0.7364522	1.626337e-01	0	0.8458089 0.273131028
404	0	0.7359755	1.629544e-01	0	0.8455036 0.273623691
405	0	0.7354983	1.632755e-01	0	0.8451979 0.274116959
406	0	0.7350205	1.635970e-01	0	0.8448918 0.274610749
407	0	0.7345406	1.639201e-01	0	0.8445842 0.275106782
408	0	0.7340583	1.642448e-01	0	0.8442751 0.275605257
409	0	0.7335739	1.645711e-01	0	0.8439645 0.276105964
410	0	0.7330867	1.648993e-01	0	0.8436520 0.276609491
411	0	0.7325971	1.652291e-01	0	0.8433380 0.277115524
412	0	0.7321049	1.655606e-01	0	0.8430225 0.277624324
413	0	0.7316122	1.658926e-01	0	0.8427065 0.278133630
414	0	0.7301298	1.668921e-01	0	0.8417552 0.279666049
415	0	0.7296350	1.672258e-01	0	0.8414376 0.280177457
416	0	0.7291395	1.675601e-01	0	0.8411193 0.280689677
417	0	0.7286436	1.678948e-01	0	0.8408007 0.281202277
418	0	0.7281477	1.682296e-01	0	0.8404821 0.281714943
419	0	0.7276494	1.685661e-01	0	0.8401618 0.282230020
420	0	0.7271465	1.689058e-01	0	0.8398384 0.282749852
421	0	0.7266358	1.692507e-01	0	0.8395103 0.283277842
422	0	0.7261245	1.695960e-01	0	0.8391816 0.283806424
423	0	0.7256132	1.699415e-01	0	0.8388528 0.284335015
424	0	0.7251011	1.702876e-01	0	0.8385235 0.284864422
425	0	0.7245826	1.706381e-01	0	0.8381899 0.285400418
426	0	0.7240630	1.709895e-01	0	0.8378555 0.285937504
427	0	0.7235430	1.713415e-01	0	0.8375205 0.286475104
428	0	0.7230222	1.716941e-01	0	0.8371849 0.287013395
429	0	0.7225001	1.720477e-01	0	0.8368483 0.287553096
430	0	0.7219651	1.724097e-01	0	0.8365038 0.288106287
431	0	0.7214239	1.727760e-01	0	0.8361553 0.288665781
432	0	0.7208828	1.731423e-01	0	0.8358069 0.289225261
433	0	0.7203394	1.735102e-01	0	0.8354568 0.289787130
434	0	0.7197932	1.738801e-01	0	0.8351049 0.290351878
435	0	0.7192420	1.742534e-01	0	0.8347497 0.290921716
436	0	0.7186870	1.746293e-01	0	0.8343922 0.291495613
437	0	0.7181248	1.750101e-01	0	0.8340300 0.292077075
438	0	0.7175606	1.753923e-01	0	0.8336664 0.292660495
439	0	0.7169867	1.757812e-01	0	0.8332965 0.293253973
440	0	0.7164069	1.761741e-01	0	0.8329228 0.293853473
441	0	0.7158221	1.765707e-01	0	0.8325456 0.294458283
442	0	0.7152370	1.769675e-01	0	0.8321682 0.295063295
443	0	0.7146515	1.773649e-01	0	0.8317902 0.295668753

444	0 0.7140644 1.777636e-01	0 0.8314109 0.296275881
445	0 0.7134650 1.781708e-01	0 0.8310236 0.296895659
446	0 0.7128564 1.785840e-01	0 0.8306306 0.297525027
447	0 0.7122461 1.789986e-01	0 0.8302363 0.298156218
448	0 0.7116297 1.794173e-01	0 0.8298382 0.298793744
449	0 0.7110053 1.798417e-01	0 0.8294346 0.299439469
450	0 0.7103804 1.802665e-01	0 0.8290305 0.300085699
451	0 0.7097549 1.806919e-01	0 0.8286260 0.300732528
452	0 0.7091032 1.811351e-01	0 0.8282046 0.301406590
453	0 0.7084374 1.815876e-01	0 0.8277745 0.302095320
454	0 0.7077636 1.820458e-01	0 0.8273389 0.302792264
455	0 0.7070794 1.825110e-01	0 0.8268966 0.303500101
456	0 0.7057098 1.834427e-01	0 0.8260110 0.304916873
457	0 0.7050209 1.839117e-01	0 0.8255652 0.305629523
458	0 0.7043315 1.843813e-01	0 0.8251188 0.306342651
459	0 0.7036366 1.848548e-01	0 0.8246687 0.307061556
460	0 0.7029382 1.853309e-01	0 0.8242162 0.307783993
461	0 0.7022389 1.858079e-01	0 0.8237627 0.308507355
462	0 0.7015347 1.862887e-01	0 0.8233056 0.309235782
463	0 0.7008304 1.867698e-01	0 0.8228482 0.309964157
464	0 0.7001131 1.872598e-01	0 0.8223824 0.310706105
465	0 0.6993882 1.877547e-01	0 0.8219120 0.311456027
466	0 0.6986603 1.882518e-01	0 0.8214395 0.312209182
467	0 0.6979031 1.887684e-01	0 0.8209488 0.312992723
468	0 0.6971118 1.893084e-01	0 0.8204358 0.313811508
469	0 0.6962932 1.898666e-01	0 0.8199057 0.314658836
470	0 0.6954186 1.904621e-01	0 0.8193405 0.315564279
471	0 0.6945063 1.910826e-01	0 0.8187518 0.316509028
472	0 0.6935844 1.917103e-01	0 0.8181562 0.317463667
473	0 0.6926582 1.923410e-01	0 0.8175578 0.318422829
474	0 0.6917242 1.929770e-01	0 0.8169545 0.319390156
475	0 0.6907807 1.936199e-01	0 0.8163446 0.320367280
476	0 0.6898069 1.942835e-01	0 0.8157151 0.321375897
477	0 0.6887704 1.949893e-01	0 0.8150459 0.322449712
478	0 0.6877078 1.957130e-01	0 0.8143598 0.323550571
479	0 0.6866384 1.964419e-01	0 0.8136687 0.324658458
480	0 0.6854859 1.972253e-01	0 0.8129267 0.325853177
481	0 0.6843289 1.980126e-01	0 0.8121808 0.327052330
482	0 0.6831613 1.988082e-01	0 0.8114270 0.328262403
483	0 0.6819291 1.996471e-01	0 0.8106326 0.329539848
484	0 0.6806885 2.004926e-01	0 0.8098318 0.330825801
485	0 0.6794017 2.013667e-01	0 0.8090048 0.332160560
486	0 0.6781116 2.022434e-01	0 0.8081755 0.333498738
487	0 0.6767027 2.031971e-01	0 0.8072745 0.334961384
488	0 0.6752556 2.041764e-01	0 0.8063495 0.336463831
489	0 0.6735257 2.053322e-01	0 0.8052620 0.338263802
490	0 0.6717619 2.065107e-01	0 0.8041534 0.340099324
491	0 0.6699386 2.077288e-01	0 0.8030081 0.341997056
492	0 0.6680666 2.089787e-01	0 0.8018334 0.343946099

```
493        0 0.6660989 2.102891e-01        0 0.8006033 0.345995995
494        0 0.6639965 2.116874e-01        0 0.7992915 0.348187099
495        0 0.6618172 2.131345e-01        0 0.7979353 0.350459451
496        0 0.6595993 2.146086e-01        0 0.7965539 0.352772125
497        0 0.6565533 2.165442e-01        0 0.7947648 0.355970720
498        0 0.6532356 2.186384e-01        0 0.7928344 0.359459298
499        0 0.6496353 2.209023e-01        0 0.7907520 0.363248699
500        0 0.6444316 2.240140e-01        0 0.7879392 0.368768014
501        0 0.6385970 2.274534e-01        0 0.7848509 0.374973439
502        0 0.6320646 2.312807e-01        0 0.7814290 0.381933398
503        0 0.6255073 2.351701e-01        0 0.7779448 0.388915109
504        0 0.6112107 2.421656e-01        0 0.7721916 0.404548460
505        0 0.5403957 2.563913e-01        0 0.7711790 0.489996898
506        0 0.5403957 2.563913e-01        0 0.7711790 0.489996898
```

From state 2 it is only possible to visit state 3 or to remain in state 2. The probability of going to state 1 is 0. The predictions $\hat{P}_{1h}(0, t)$ from state 1 in [[1]] are perhaps of most interest here.

```
> summary(pt, from = 1)

Prediction from state 1 (head and tail):
          time    pstate1       pstate2       pstate3            se1           se2
1 0.000000000 1.0000000 0.0000000000 0.0000000000 0.0000000000 0.0000000000
2 0.002737851 0.9991669 0.0005277714 0.0003053084 0.0006117979 0.0005285695
3 0.008213552 0.9986390 0.0010556490 0.0003053084 0.0008100529 0.0007492497
4 0.010951403 0.9983340 0.0010554282 0.0006106022 0.0008685356 0.0007490930
5 0.016427105 0.9977235 0.0010549862 0.0012215589 0.0009807157 0.0007487794
6 0.019164956 0.9965843 0.0015830048 0.0018327183 0.0012115670 0.0009191199
           se3    lower1       lower2       lower3     upper1      upper2
1 0.0000000000 1.0000000 0.000000e+00 0.000000e+00 1.0000000 0.000000000
2 0.0003082357 0.9979685 7.412369e-05 4.220615e-05 1.0000000 0.003757809
3 0.0003082357 0.9970526 2.626497e-04 4.220615e-05 1.0000000 0.004242894
4 0.0004401329 0.9966331 2.625948e-04 1.486610e-04 1.0000000 0.004242006
5 0.0006342283 0.9958031 2.624848e-04 4.415441e-04 0.9996475 0.004240230
6 0.0007908588 0.9942125 5.072942e-04 7.866531e-04 0.9989617 0.004939745
       upper3
1 0.000000000
2 0.002208522
3 0.002208522
4 0.002507954
5 0.003379518
6 0.004269806


...
        time   pstate1   pstate2   pstate3        se1        se2        se3
501 6.253251 0.2308531 0.4336481 0.3354989 0.02448884 0.02974526 0.03063866
502 6.357290 0.2283925 0.4304829 0.3411246 0.02460675 0.03002904 0.03150500
503 6.362765 0.2259175 0.4272883 0.3467942 0.02472281 0.03031296 0.03234850
504 6.798084 0.2209174 0.4208123 0.3582703 0.02518284 0.03119272 0.03507050
505 7.110198 0.2014549 0.3954248 0.4031203 0.03067690 0.03987257 0.05867417
```

```
506 7.731691 0.2014549 0.3954248 0.4031203 0.03067690 0.03987257 0.05867417
        lower1    lower2    lower3    upper1    upper2    upper3
501 0.1875169 0.3790974 0.2805156 0.2842045 0.4960483 0.4012593
502 0.1849160 0.3754732 0.2846421 0.2820911 0.4935519 0.4088150
503 0.1823058 0.3718215 0.2888504 0.2799621 0.4910294 0.4163617
504 0.1766850 0.3639092 0.2957250 0.2762233 0.4866130 0.4340438
505 0.1494719 0.3245138 0.3030695 0.2715164 0.4818309 0.5362003
506 0.1494719 0.3245138 0.3030695 0.2715164 0.4818309 0.5362003
```

But we see that we do not have enough information to create Figure 15 of the tutorial, since the probability of the relapse/death state (`pstate3`) does not distinguish between relapse/death before or after platelet recovery. The remedy is actually easy in this case. Consider a different multi-state model with two RelDeath states, the first one (state 3) after platelet recovery, the second one (state 4) without platelet recovery. The transition matrix of this multi-state model is defined as

```
> tmat2 <- transMat(x = list(c(2, 4), c(3), c(), c()))
> tmat2

        to
from     State 1 State 2 State 3 State 4
  State 1      NA       1      NA       2
  State 2      NA      NA       3      NA
  State 3      NA      NA      NA      NA
  State 4      NA      NA      NA      NA
```

The multi-state model has four states and the same three transitions as before. If we apply *probtrans* to this new multi-state model with the same estimated cumulative hazards and standard errors as before, we get exactly what we want. Thus, we just have to call *probtrans* with the old `msf2` and the new `tmat2`. From version 0.2.3 on, since the transition matrix is in the *msfit* object, we just need to replace the `trans` item of `msf2` by `tmat2`. In the elements of the resulting lists, `pstate3` will indicate the probability of relapse/death after platelet recovery and `pstate4` the probability of relapse/death without platelet recovery.

```
> msf2$trans <- tmat2
> pt <- probtrans(msf2, predt = 0)
> summary(pt, from = 1)

Prediction from state 1 (head and tail):
          time    pstate1      pstate2       pstate3       pstate4          se1
1 0.000000000 1.0000000 0.0000000000 0.000000e+00 0.0000000000 0.0000000000
2 0.002737851 0.9991669 0.0005277714 0.000000e+00 0.0003053084 0.0006117979
3 0.008213552 0.9986390 0.0010556490 0.000000e+00 0.0003053084 0.0008100529
4 0.010951403 0.9983340 0.0010554282 2.208393e-07 0.0006103813 0.0008685356
5 0.016427105 0.9977235 0.0010549862 6.628276e-07 0.0012208961 0.0009807157
6 0.019164956 0.9965843 0.0015830048 1.105048e-06 0.0018316132 0.0012115670
          se2          se3          se4    lower1       lower2       lower3
1 0.0000000000 0.000000e+00 0.0000000000 1.0000000 0.000000e+00 0.000000e+00
2 0.0005285695 1.116923e-07 0.0003080762 0.9979685 7.412369e-05 0.000000e+00
3 0.0007492497 1.116923e-07 0.0003080762 0.9970526 2.626497e-04 0.000000e+00
4 0.0007490930 2.989514e-07 0.0004397978 0.9966331 2.625948e-04 1.555250e-08
```

```
5 0.0007487794 6.308958e-07 0.0006336859 0.9958031 2.624848e-04 1.026138e-07
6 0.0009191199 1.032427e-06 0.0007900509 0.9942125 5.072942e-04 1.770590e-07
          lower4     upper1      upper2        upper3      upper4
1 0.0000000000 1.0000000 0.000000000 0.000000e+00 0.000000000
2 0.0000422494 1.0000000 0.003757809          NaN 0.002206261
3 0.0000422494 1.0000000 0.004242894          NaN 0.002206261
4 0.0001486912 1.0000000 0.004242006 3.135832e-06 0.002505631
5 0.0004414450 0.9996475 0.004240230 4.281495e-06 0.003376609
6 0.0007864573 0.9989617 0.004939745 6.896741e-06 0.004265720


...
        time    pstate1   pstate2   pstate3   pstate4         se1         se2
501 6.253251 0.2308531 0.4336481 0.1681264 0.1673724 0.02448884 0.02974526
502 6.357290 0.2283925 0.4304829 0.1712916 0.1698330 0.02460675 0.03002904
503 6.362765 0.2259175 0.4272883 0.1744862 0.1723080 0.02472281 0.03031296
504 6.798084 0.2209174 0.4208123 0.1809622 0.1773081 0.02518284 0.03119272
505 7.110198 0.2014549 0.3954248 0.2063497 0.1967706 0.03067690 0.03987257
506 7.731691 0.2014549 0.3954248 0.2063497 0.1967706 0.03067690 0.03987257
           se3        se4     lower1    lower2    lower3    lower4    upper1
501 0.02379684 0.02100629 0.1875169 0.3790974 0.1273960 0.1308738 0.2842045
502 0.02430502 0.02136056 0.1849160 0.3754732 0.1297050 0.1327282 0.2820911
503 0.02480762 0.02170882 0.1823058 0.3718215 0.1320509 0.1346059 0.2799621
504 0.02616939 0.02264879 0.1766850 0.3639092 0.1362993 0.1380380 0.2762233
505 0.03690104 0.02987965 0.1494719 0.3245138 0.1453401 0.1461185 0.2715164
506 0.03690104 0.02987965 0.1494719 0.3245138 0.1453401 0.1461185 0.2715164
       upper2    upper3    upper4
501 0.4960483 0.2218790 0.2140499
502 0.4935519 0.2262118 0.2173106
503 0.4910294 0.2305584 0.2205703
504 0.4866130 0.2402604 0.2277500
505 0.4818309 0.2929694 0.2649813
506 0.4818309 0.2929694 0.2649813
```

The reader may check that the `pstate3` and `pstate4` probabilities of this new Aalen-Johansen estimator sum up to the `pstate3` probability of the result of the previous call to *probtrans*, and that the `pstate1` and `pstate2` probabilities are unchanged.

Figure 2 contains a plot of `pt1`. For this we use the `plot` method for *probtrans* objects.

```
> plot(pt, ord = c(2, 3, 4, 1), lwd = 2, xlab = "Years since transplant",
+     ylab = "Prediction probabilities", cex = 0.75, legend = c("Alive in remission, no PR",
+         "Alive in remission, PR", "Relapse or death after PR",
+         "Relapse or death without PR"))
```

The argument *from* determines from which state the transition probabilities are to be plotted. The default is from state 1, which is what we want, so the *from* argument is omitted here. The default *type* of the `plot` method for *probtrans* objects is a "stacked" plot, for which the difference between two adjacent lines represents the probability of being in a state. The argument *ord* specifies the order of the states of which the probabilities are stacked. The present order, 2, 3, 4, 1, allows states 2 and 3 to be combined visually (states with platelet recovery) and states 3 and 4 (death states). Other plot types are "filled", which is like "stacked", but uses colors
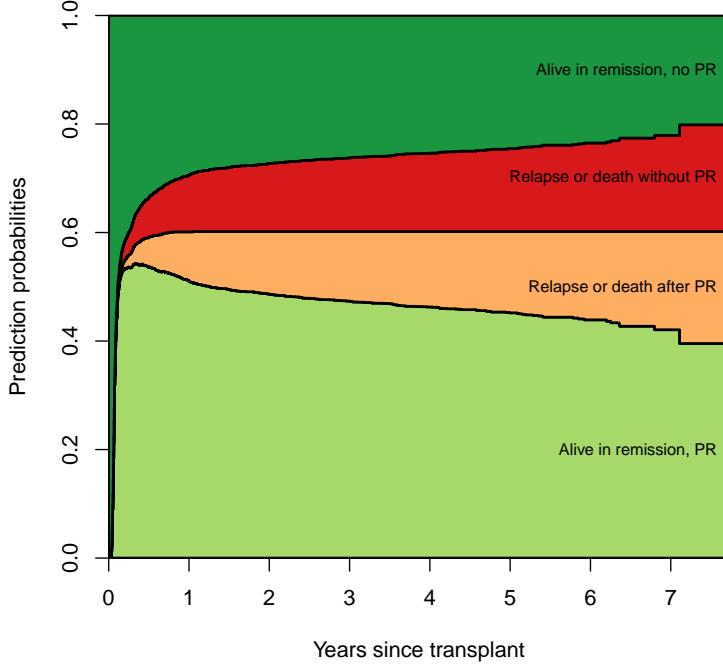
Figure 2: Stacked prediction probabilities at $s = 0$ for a reference patient. PR stands for platelet recovery

to fill the space between adjacent lines, "single", which simply plots the transition probabilities as different lines in a single plot, and "separate", which uses separate plots for the transition probabilities.

To obtain the predictions $\hat{P}_{1h}(s, t)$ for $s = 0.5$, which are plotted in Figure 16 of the tutorial, we simply change the value of *predt* in the call to `probtrans`.

```
> pt <- probtrans(msf2, predt = 0.5)
> summary(pt, from = 1)

Prediction from state 1 (head and tail):
        time    pstate1     pstate2      pstate3     pstate4         se1
1 0.5000000 1.0000000 0.000000000 0.000000e+00 0.000000000 0.000000000
2 0.5010267 0.9985898 0.000000000 0.000000e+00 0.001410218 0.003237571
3 0.5037645 0.9976488 0.000000000 0.000000e+00 0.002351164 0.004183373
4 0.5065024 0.9955387 0.001639506 0.000000e+00 0.002821775 0.006169060
5 0.5092402 0.9938957 0.003282495 0.000000e+00 0.002821775 0.007422321
6 0.5119781 0.9915469 0.003277183 5.312169e-06 0.005170580 0.008513835
          se2          se3         se4    lower1       lower2      lower3
1 0.000000000 0.000000e+00 0.000000000 1.0000000 0.000000e+00 0.0000e+00
2 0.000000000 0.000000e+00 0.003237571 0.9922644 0.000000e+00 0.0000e+00
3 0.000000000 0.000000e+00 0.004183373 0.9894832 0.000000e+00 0.0000e+00
4 0.004136138 2.101143e-06 0.004583357 0.9835207 1.167630e-05 0.0000e+00
5 0.005848968 2.101143e-06 0.004583357 0.9794542 9.987955e-05 0.0000e+00
6 0.005839510 1.353036e-05 0.006209919 0.9749997 9.971745e-05 3.6076e-08
```

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```
          lower4 upper1    upper2       upper3     upper4
1 0.000000e+00      1 0.0000000 0.0000000000 0.00000000
2 1.567120e-05      1 0.0000000 0.0000000000 0.12690255
3 7.190497e-05      1 0.0000000 0.0000000000 0.07687883
4 1.169315e-04      1 0.2302081          NaN 0.06809471
5 1.169315e-04      1 0.1078777          NaN 0.06809471
6 4.911765e-04      1 0.1077036 0.0007822136 0.05443032


...
          time    pstate1    pstate2     pstate3   pstate4         se1        se2
330 6.253251 0.6872018 0.02597812 0.005991102 0.2808290 0.05248379 0.01448894
331 6.357290 0.6798772 0.02578851 0.006180714 0.2881535 0.05348008 0.01438691
332 6.362765 0.6725095 0.02559713 0.006372091 0.2955212 0.05445049 0.01428397
333 6.798084 0.6576254 0.02520918 0.006760043 0.3104053 0.05723289 0.01407791
334 7.110198 0.5996895 0.02368832 0.008280903 0.3683412 0.07993696 0.01332734
335 7.731691 0.5996895 0.02368832 0.008280903 0.3683412 0.07993696 0.01332734
             se3        se4    lower1     lower2      lower3    lower4
330 0.003565503 0.05117341 0.5916642 0.008706862 0.001866073 0.1964870
331 0.003675647 0.05224080 0.5827386 0.008640867 0.001926781 0.2019786
332 0.003786522 0.05327926 0.5738257 0.008574230 0.001988236 0.2075517
333 0.004019125 0.05620683 0.5544966 0.008437438 0.002108021 0.2176694
334 0.005060910 0.07944552 0.4618104 0.007863898 0.002499552 0.2413567
335 0.005060910 0.07944552 0.4618104 0.007863898 0.002499552 0.2413567
        upper1     upper2     upper3     upper4
330 0.7981661 0.07750930 0.01923468 0.4013749
331 0.7932082 0.07696533 0.01982645 0.4110953
332 0.7881646 0.07641656 0.02042190 0.4207761
333 0.7799349 0.07531940 0.02167824 0.4426505
334 0.7787343 0.07135602 0.02743426 0.5621360
335 0.7787343 0.07135602 0.02743426 0.5621360
```

The result now contains only time points $t \geq 0.5$. Figure 3 contains a plot of pt1.

```
> plot(pt, ord = c(2, 3, 4, 1), lwd = 2, xlab = "Years since transplant",
+     ylab = "Prediction probabilities", cex = 0.75, legend = c("Alive in remission, no PR",
+         "Alive in remission, PR", "Relapse or death after PR",
+         "Relapse or death without PR"))
```

Figure 17 of the tutorial distinguishes between three patients, one being the good old (or rather young) reference patient, for which we have already calculated the probabilities, one for a patient in the age category 20-40, and one for a patient older than 40. To obtain prediction probabilities for the latter two patients as well, we have to repeat part of the calculations, changing only the value of age in the newdata data frame.

```
> msf2$trans <- tmat
> msf.20 <- msf2 # copy msfit result for reference (young) patient
> newd <- newd[,1:5] # use the basic covariates of the reference patient
> newd2 <- newd
> newd2$age <- 1
> newd2$age <- factor(newd2$age,levels=0:2,labels=levels(ebmt3$age))
> attr(newd2, "trans") <- tmat
```
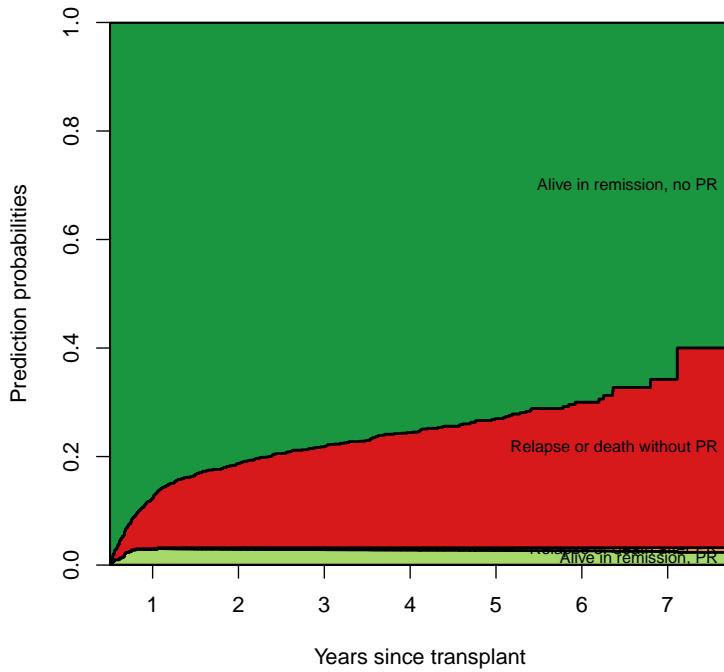
Figure 3: Stacked prediction probabilities at $s = 0.5$ for a reference patient

```
> class(newd2) <- c("msdata","data.frame")
> newd2 <- expand.covs(newd2,covs[1:4],longnames=FALSE)
> newd2$strata=c(1,2,2)
> newd2$pr <- c(0,0,1)
> msf.2040 <- msfit(c2, newdata=newd2, trans=tmat)
> newd3 <- newd
> newd3$age <- 2
> newd3$age <- factor(newd3$age,levels=0:2,labels=levels(ebmt3$age))
> attr(newd3, "trans") <- tmat
> class(newd3) <- c("msdata","data.frame")
> newd3 <- expand.covs(newd3,covs[1:4],longnames=FALSE)
> newd3$strata=c(1,2,2)
> newd3$pr <- c(0,0,1)
> msf.40 <- msfit(c2, newdata=newd3, trans=tmat)
> pt.20 <- probtrans(msf.20,predt=0) # original young (<= 20) patient
> pt.201 <- pt.20[[1]]; pt.202 <- pt.20[[2]]
> pt.2040 <- probtrans(msf.2040,predt=0) # patient 20-40
> pt.20401 <- pt.2040[[1]]; pt.20402 <- pt.2040[[2]]
> pt.40 <- probtrans(msf.40,predt=0) # patient > 40
> pt.401 <- pt.40[[1]]; pt.402 <- pt.40[[2]]
```

The 5-years transition probabilities $P_{13}(0, 5)$ and $P_{23}(0, 5)$ are estimated as 0.30275 and 0.26210 respectively.

```
> pt.201[488:489,] # 5 years falls between 488th and 489th time point
```

```
       time   pstate1   pstate2   pstate3        se1        se2        se3
488 4.985626 0.2452605 0.4519872 0.3027523 0.02411439 0.02853645 0.02693539
489 5.084189 0.2445602 0.4511034 0.3043365 0.02412385 0.02858110 0.02707436
```

```
> pt.202[488:489,] # 5-years probabilities
```

```
       time pstate1   pstate2   pstate3 se1        se2        se3
488 4.985626       0 0.7378970 0.2621030   0 0.03339911 0.03339911
489 5.084189       0 0.7364541 0.2635459   0 0.03356217 0.03356217
```

Figure 4 shows relapse-free survival probabilities without distinction between before or after platelet recovery, so we can use the first transition matrix `tmat`. The probabilities we want are $1 - \hat{P}_{13}(0, t)$ and $1 - \hat{P}_{23}(0, t)$, the first one conditioning on being in state 1 (transplantation, i.e. no PR), the second in being in state 2 (PR).

```
> plot(pt.201$time, 1 - pt.201$pstate3, ylim = c(0.425, 1), type = "s",
+     lwd = 2, col = "red", xlab = "Years since transplant", ylab = "Relapse-free survival")
> lines(pt.20401$time, 1 - pt.20401$pstate3, type = "s", lwd = 2,
+     col = "blue")
> lines(pt.401$time, 1 - pt.401$pstate3, type = "s", lwd = 2, col = "green")
> lines(pt.202$time, 1 - pt.202$pstate3, type = "s", lwd = 2, col = "red",
+     lty = 2)
> lines(pt.20402$time, 1 - pt.20402$pstate3, type = "s", lwd = 2,
+     col = "blue", lty = 2)
> lines(pt.402$time, 1 - pt.402$pstate3, type = "s", lwd = 2, col = "green",
+     lty = 2)
> legend(6, 1, c("no PR", "PR"), lwd = 2, lty = 1:2, xjust = 1,
+     bty = "n")
> legend("topright", c("<=20", "20-40", ">40"), lwd = 2, col = c("red",
+     "blue", "green"), bty = "n")
```

It is also possible to do prediction with a fixed horizon. This should not be understood as attempting to predict the past. It means that in our prediction probabilities $P_{gh}(s, t)$, we fix t, a time horizon, and we want to study how $P_{gh}(s, t)$ changes as more and more information on a patient becomes available. From a computational point of view this just means that the order of the matrix multiplication in (2) is reversed. We will plot $1 - \hat{P}_{13}(s, 5)$ and $1 - \hat{P}_{23}(s, 5)$, the 5-years relapse-free survival probabilities given that the patient is in state 1 (no PR) and in state 2 (PR), respectively, for the same three patients as before.

```
> pt.20 <- probtrans(msf.20, direction = "fixedhorizon", predt = 5)
> pt.201 <- pt.20[[1]]
> pt.202 <- pt.20[[2]]
> head(pt.201)
```

```
          time   pstate1   pstate2   pstate3        se1        se2        se3
1 0.000000000 0.2452605 0.4519872 0.3027523 0.02411439 0.02853645 0.02693539
2 0.002737851 0.2454650 0.4519742 0.3025608 0.02413403 0.02854695 0.02694328
3 0.008213552 0.2455948 0.4518230 0.3025823 0.02414644 0.02854909 0.02694380
4 0.010951403 0.2456698 0.4519611 0.3023691 0.02415369 0.02855746 0.02695114
5 0.016427105 0.2458201 0.4522376 0.3019422 0.02416821 0.02857418 0.02696574
6 0.019164956 0.2461011 0.4523628 0.3015361 0.02419520 0.02859303 0.02698076
```
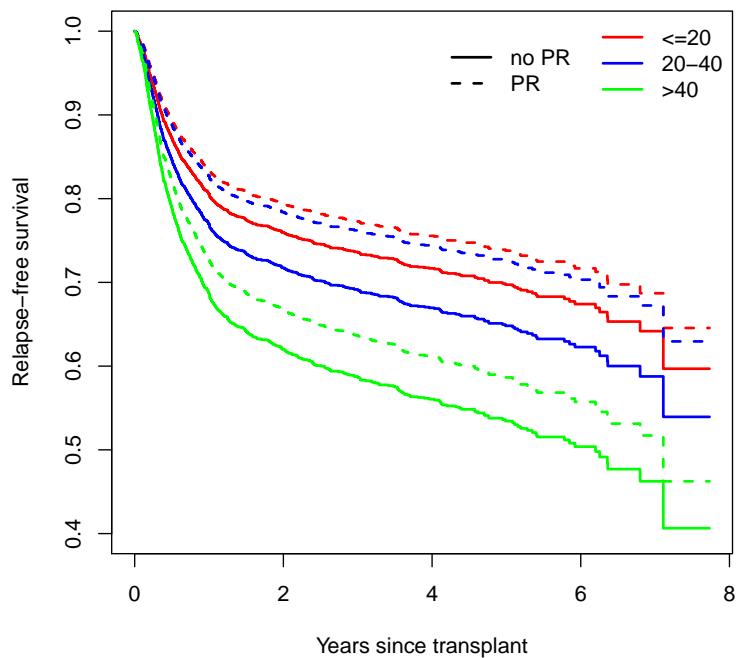
Figure 4: Predicted relapse-free survival probabilities for three patients in different age categories, given platelet recovery (dashed) and given no platelet recovery (solid). The time of prediction was at transplant (note: in the tutorial this was at 1 month after transplant).

```
> head(pt.202)
```

	time	pstate1	pstate2	pstate3	se1	se2	se3
1	0.000000000	0	0.7378970	0.2621030	0	0.03339911	0.03339911
2	0.002737851	0	0.7380513	0.2619487	0	0.03340572	0.03340572
3	0.008213552	0	0.7380513	0.2619487	0	0.03340572	0.03340572
4	0.010951403	0	0.7382057	0.2617943	0	0.03341233	0.03341233
5	0.016427105	0	0.7385150	0.2614850	0	0.03342551	0.03342551
6	0.019164956	0	0.7388247	0.2611753	0	0.03343863	0.03343863

Here item [[1]] gives estimates $\hat{P}_{1h}(s,5)$ and [[2]] gives estimates $\hat{P}_{2h}(s,5)$. For item [[g]], the column time gives the different values of s and pstate1 etc give the estimated probabilities of being in state 1 etc at 5 years, conditional on being in state g at time s. In pt.201 we recognize at time (s)=0) 0.30275 as $\hat{P}_{1h}(0,5)$ and in pt.202 we see 0.26210 as $\hat{P}_{2h}(0,5)$. The backward transition probabilities for the other two patients are calculated similarly.

```
> pt.2040 <- probtrans(msf.2040, direction = "fixedhorizon", predt = 5)
> pt.20401 <- pt.2040[[1]]
> pt.20402 <- pt.2040[[2]]
> pt.40 <- probtrans(msf.40, direction = "fixedhorizon", predt = 5)
> pt.401 <- pt.40[[1]]
> pt.402 <- pt.40[[2]]
```

As mentioned before, in $s = 0$, these probabilities are the same as the five-years probabilities of Figure 4, and as s approaches 5, the probabilities approach 1, since both $\hat{P}_{13}(s,5)$ and $\hat{P}_{23}(s,5)$ approach 0. Figure 5 shows 5-years relapse-free survival probabilities, both with and without platelet recovery, with the prediction time s varying.

```
> plot(pt.201$time, 1 - pt.201$pstate3, ylim = c(0.425, 1), type = "s",
+     lwd = 2, col = "red", xlab = "Years since transplant", ylab = "Relapse-free survival")
> lines(pt.20401$time, 1 - pt.20401$pstate3, type = "s", lwd = 2,
+     col = "blue")
> lines(pt.401$time, 1 - pt.401$pstate3, type = "s", lwd = 2, col = "green")
> lines(pt.202$time, 1 - pt.202$pstate3, type = "s", lwd = 2, col = "red",
+     lty = 2)
> lines(pt.20402$time, 1 - pt.20402$pstate3, type = "s", lwd = 2,
+     col = "blue", lty = 2)
> lines(pt.402$time, 1 - pt.402$pstate3, type = "s", lwd = 2, col = "green",
+     lty = 2)
> legend("topleft", c("<=20", "20-40", ">40"), lwd = 2, col = c("red",
+     "blue", "green"), bty = "n")
> legend(1, 1, c("no PR", "PR"), lwd = 2, lty = 1:2, bty = "n")
> title(main = "Backward prediction")
```

5 Competing risks

The data used in Section 3 of the tutorial is available in *mstate* under the name aidssi. See the help file for more information.

```
> data(aidssi)
> si <- aidssi # Just a shorter name
> head(si)
```

Backward prediction
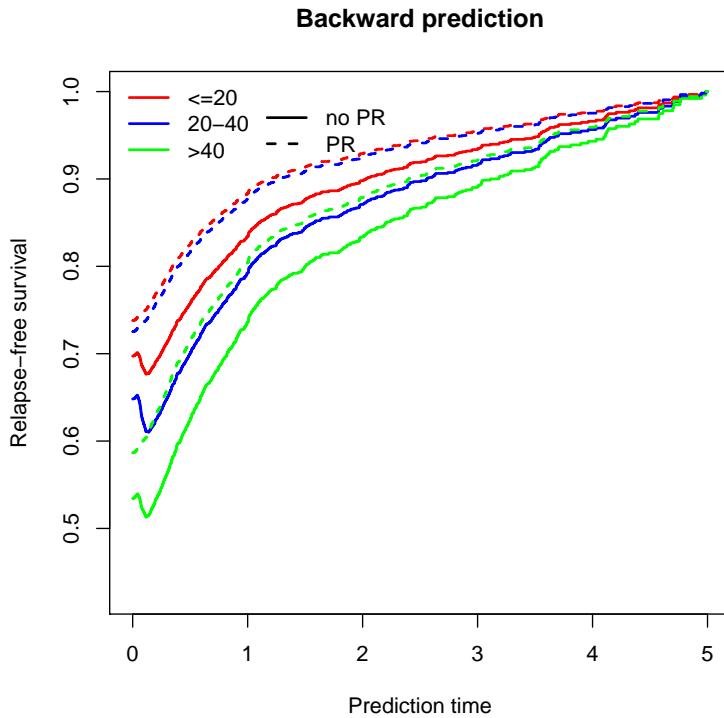
Figure 5: Predicted probabilities of 5-years relapse-free survival, conditional on being alive without relapse with (PR) and without platelet recovery (no PR). Patients in three age categories.

```
  patnr   time status      cause ccr5
1     1  9.106      1       AIDS   WW
2     2 11.039      0 event-free   WM
3     3  2.234      1       AIDS   WW
4     4  9.878      2         SI   WM
5     5  3.819      1       AIDS   WW
6     6  6.801      1       AIDS   WW

> table(si$status)

  0   1   2
107 114 108
```

To prepare data in long format, it is possible to use *msprep*. In this case there is not a huge advantage in using *msprep*; the long data may just as easily be prepared directly. Nevertheless we will illustrate the use of *msprep* to obtain data in long format. The function *trans.comprisk* prepares a transition matrix for competing risks models. The first argument is the number of causes of failure; in the *names* argument a character vector of length three (the total number of states in the multi-state model including the failure-free state) may be given. The transition matrix has three states with stte 1 being the failure-free state and the subsequent sttes representing the different causes of failure.

```
> tmat <- trans.comprisk(2, names = c("event-free", "AIDS", "SI"))
> tmat
```

```
           to
from           event-free AIDS SI
  event-free          NA    1  2
  AIDS                NA   NA NA
  SI                  NA   NA NA
```

Now follows the actual call to *msprep*.

```
> si$stat1 <- as.numeric(si$status == 1)
> si$stat2 <- as.numeric(si$status == 2)
> silong <- msprep(time = c(NA, "time", "time"), status = c(NA,
+     "stat1", "stat2"), data = si, keep = "ccr5", trans = tmat)
```

We can use *events* to check whether the number of events from original data (si) corresponds with long data.

```
> events(silong)
```

```
$Frequencies
           to
from           event-free AIDS  SI no event total entering
  event-free          0  114 108      107              329
  AIDS                0    0   0      114              114
  SI                  0    0   0      108              108
```

```
$Proportions
           to
from        event-free       AIDS        SI  no event
  event-free  0.0000000 0.3465046 0.3282675 0.3252280
  AIDS        0.0000000 0.0000000 0.0000000 1.0000000
  SI          0.0000000 0.0000000 0.0000000 1.0000000
```

For the regression analyses to be performed later we add transition-specific covariates. In the context of competing risks one could call them cause-specific covariates. Since the factor levels of CCR5 are quite short we keep the default setting (TRUE) of *longnames*.

```
> silong <- expand.covs(silong, "ccr5")
> silong[1:8, ]
```

```
An object of class 'msdata'
```

```
Data:
  id from to trans Tstart  Tstop   time status ccr5 ccr5WM.1 ccr5WM.2
1  1    1  2     1      0  9.106  9.106      1   WW        0        0
2  1    1  3     2      0  9.106  9.106      0   WW        0        0
3  2    1  2     1      0 11.039 11.039      0   WM        1        0
4  2    1  3     2      0 11.039 11.039      0   WM        0        1
5  3    1  2     1      0  2.234  2.234      1   WW        0        0
6  3    1  3     2      0  2.234  2.234      0   WW        0        0
7  4    1  2     1      0  9.878  9.878      0   WM        1        0
8  4    1  3     2      0  9.878  9.878      1   WM        0        1
```

To illustrate the fact that naive Kaplan-Meiers are biased estimators of the probabilities of failing from the different causes of failure, we just make use of the functions in the *survival* package. I am using `coxph` below, probably this could be done quicker.

```
> c1 <- coxph(Surv(time, status) ~ 1, data = silong, subset = (trans ==
+     1), method = "breslow")
> c2 <- coxph(Surv(time, status) ~ 1, data = silong, subset = (trans ==
+     2), method = "breslow")
> h1 <- survfit(c1)
> h1 <- data.frame(time = h1$time, surv = h1$surv)
> h2 <- survfit(c2)
> h2 <- data.frame(time = h2$time, surv = h2$surv)
```

These naive Kaplan-Meier curves are shown in Figure 6 (Figure 2 in the tutorial). The Kaplan-Meier estimate of AIDS is plotted as a survival curve, while that of SI appearance is shown as a distribution function. There is some extra code to chop the time at 13 years. This was just done to make the picture prettier.

```
> idx1 <- (h1$time<13) # this restricts the plot to the first 13 years
> plot(c(0,h1$time[idx1],13),c(1,h1$surv[idx1],min(h1$surv[idx1])),type="s",
+     xlim=c(0,13),ylim=c(0,1),xlab="Years from HIV infection",ylab="Probability",lwd=2)
> idx2 <- (h2$time<13)
> lines(c(0,h2$time[idx2],13),c(0,1-h2$surv[idx2],max(1-h2$surv[idx2])),type="s",lwd=2)
> text(8,0.71,adj=0,"AIDS")
> text(8,0.32,adj=0,"SI")
```

Cumulative incidence functions can be computed using the function `Cuminc`. It takes as main arguments *time* and *status*, which can be provided as vectors

```
> ci <- Cuminc(time = si$time, status = si$status)
```

or, alternatively, as column names representing time and status, along with a *data* argument containing these column names.

```
> ci <- Cuminc(time = "time", status = "status", data = aidssi)
```

The result is a data frame containing the failure-free probabilities (`Surv`) and the cumulative incidence functions with their standard errors. Other arguments allow to specify the codes for the causes of failure and a group identifier.

```
> head(ci)
```

	time	Surv	CI.1	CI.2	seSurv	seCI.1	seCI.2
1	0.112	0.9969605	0	0.003039514	0.003034891	0	0.003034891
2	0.137	0.9939210	0	0.006079027	0.004285436	0	0.004285436
3	0.474	0.9908628	0	0.009137246	0.005251290	0	0.005251290
4	0.824	0.9877760	0	0.012224046	0.006074796	0	0.006074796
5	0.884	0.9846795	0	0.015320522	0.006799283	0	0.006799283
6	0.969	0.9815830	0	0.018416998	0.007449696	0	0.007449696

```
> tail(ci)
```
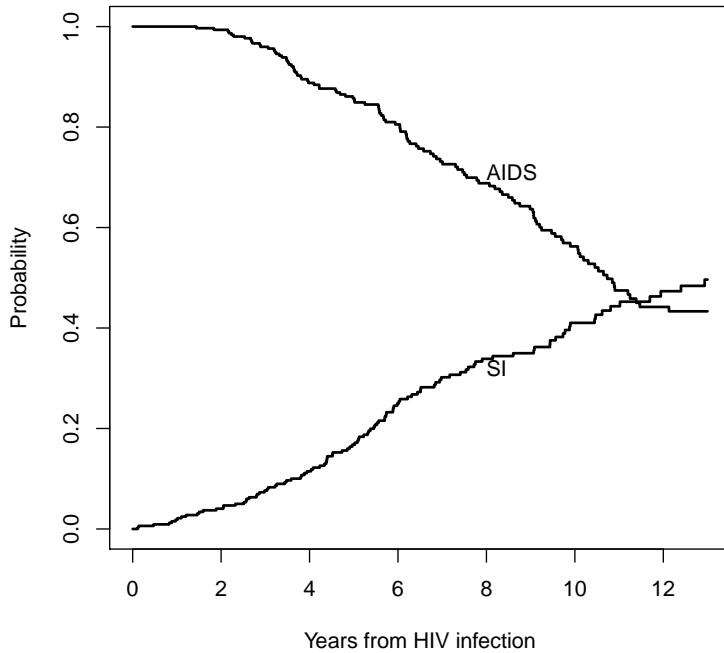
Figure 6: Estimated survival curve for AIDS and probability of SI appearance, based on the naive Kaplan-Meier estimator.

```
        time      Surv      CI.1      CI.2     seSurv     seCI.1     seCI.2
211 11.943 0.2312339 0.4035707 0.3651954 0.02638091 0.02978948 0.02881464
212 12.129 0.2266092 0.4081954 0.3651954 0.02625552 0.02989297 0.02881464
213 12.400 0.2219845 0.4081954 0.3698201 0.02612382 0.02989297 0.02896110
214 12.936 0.2165702 0.4081954 0.3752344 0.02604167 0.02989297 0.02919663
215 13.361 0.2067261 0.4180395 0.3752344 0.02665370 0.03089977 0.02919663
216 13.936 0.0000000 0.4180395 0.5819605 0.00000000 0.03089977 0.03089977
```

The cumulative incidence functions just obtained can be used to reproduce Figure 3 of the tutorial. The plots are shown in Figure 7.

```
> idx0 <- (ci$time < 13)
> plot(c(0, ci$time[idx0], 13), c(1, 1 - ci$CI.1[idx0], min(1 -
+     ci$CI.1[idx0])), type = "s", xlim = c(0, 13), ylim = c(0,
+     1), xlab = "Years from HIV infection", ylab = "Probability",
+     lwd = 2)
> idx1 <- (h1$time < 13)
> lines(c(0, h1$time[idx1], 13), c(1, h1$surv[idx1], min(h1$surv[idx1])),
+     type = "s", lwd = 2, col = 8)
> lines(c(0, ci$time[idx0], 13), c(0, ci$CI.2[idx0], max(ci$CI.2[idx0])),
+     type = "s", lwd = 2)
> idx2 <- (h2$time < 13)
> lines(c(0, h2$time[idx2], 13), c(0, 1 - h2$surv[idx2], max(1 -
+     h2$surv[idx2])), type = "s", lwd = 2, col = 8)
```
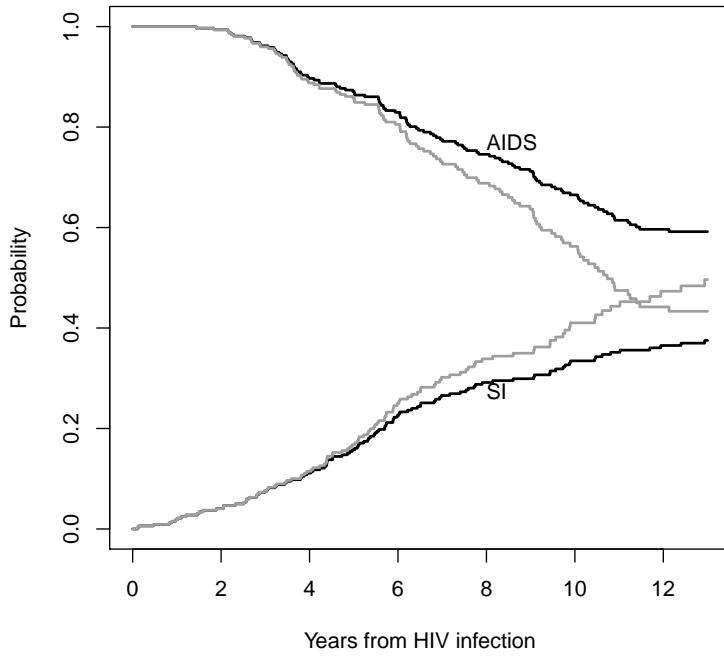
Figure 7: Estimates of probabilities of AIDS and SI appearance, based on the naive Kaplan-Meier (grey) and on cumulative incidence functions (black).

```
> text(8, 0.77, adj = 0, "AIDS")
> text(8, 0.275, adj = 0, "SI")
```

The stacked plots of Figure 4 of the tutorial are shown in Figure 8.

```
> idx0 <- (ci$time < 13)
> plot(c(0, ci$time[idx0]), c(0, ci$CI.1[idx0]), type = "s", xlim = c(0,
+     13), ylim = c(0, 1), xlab = "Years from HIV infection", ylab = "Probability",
+     lwd = 2)
> lines(c(0, ci$time[idx0]), c(0, ci$CI.1[idx0] + ci$CI.2[idx0]),
+     type = "s", lwd = 2)
> text(13, 0.5 * max(ci$CI.1[idx0]), adj = 1, "AIDS")
> text(13, max(ci$CI.1[idx0]) + 0.5 * max(ci$CI.2[idx0]), adj = 1,
+     "SI")
> text(13, 0.5 + 0.5 * max(ci$CI.1[idx0]) + 0.5 * max(ci$CI.2[idx0]),
+     adj = 1, "Event-free")
```

Regression

The section on regression in the tutorial already shows some R code and occasional output. Because of the fact that I used *msprep* to prepare the long data, occasionally there will be very small differences with the code in the tutorial. We start with regression on cause-specific hazards. Using the original dataset, we can apply ordinary Cox regression for cause 1 (AIDS), taking only the AIDS cases as events. This is done by specifying status==1 below (observations
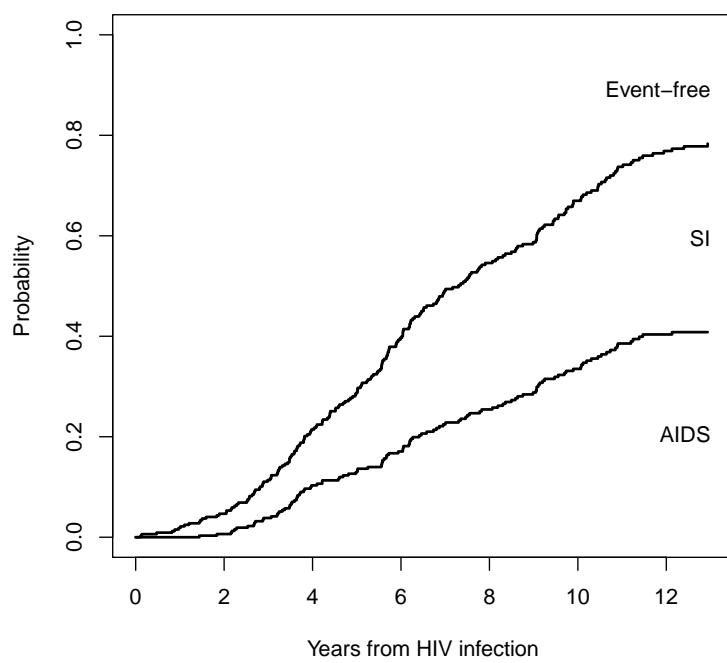
Figure 8: Cumulative incidence curves of AIDS and SI appearance. The cumulative incidence functions are stacked; the distances between two curves represent the probabilities of the different events.

with status=0 (true censorings) and status=2 (SI) are treated as censorings). Similarly for cause 2 (SI appearance), where `status==2` indicates that only failures due to SI appearance are to be treated as events.

```
> coxph(Surv(time, status == 1) ~ ccr5, data = si) # AIDS

Call:
coxph(formula = Surv(time, status == 1) ~ ccr5, data = si)


          coef exp(coef) se(coef)      z        p
ccr5WM -1.2358    0.2906   0.3071 -4.024 5.72e-05

Likelihood ratio test=21.98  on 1 df, p=2.756e-06
n= 324, number of events= 113
   (5 observations deleted due to missingness)

> coxph(Surv(time, status == 2) ~ ccr5, data = si) # SI appearance

Call:
coxph(formula = Surv(time, status == 2) ~ ccr5, data = si)


          coef exp(coef) se(coef)      z     p
ccr5WM -0.2542    0.7755   0.2380 -1.068 0.286

Likelihood ratio test=1.19  on 1 df, p=0.2748
n= 324, number of events= 107
   (5 observations deleted due to missingness)
```

The same analysis can be performed using the long format dataset `silong` in several ways. For instance, as separate Cox regressions.

```
> coxph(Surv(time, status) ~ ccr5, data = silong, subset = (trans ==
+     1), method = "breslow")

Call:
coxph(formula = Surv(time, status) ~ ccr5, data = silong, subset = (trans ==
    1), method = "breslow")


          coef exp(coef) se(coef)      z        p
ccr5WM -1.2358    0.2906   0.3071 -4.024 5.73e-05

Likelihood ratio test=21.98  on 1 df, p=2.758e-06
n= 324, number of events= 113
   (5 observations deleted due to missingness)

> coxph(Surv(time, status) ~ ccr5, data = silong, subset = (trans ==
+     2), method = "breslow")

Call:
coxph(formula = Surv(time, status) ~ ccr5, data = silong, subset = (trans ==
    2), method = "breslow")
```

```
            coef exp(coef) se(coef)      z     p
ccr5WM -0.2542     0.7755   0.2380 -1.068 0.286

Likelihood ratio test=1.19  on 1 df, p=0.2748
n= 324, number of events= 107
   (5 observations deleted due to missingness)
```

And in a single analysis, using the expanded covariates.

```
> coxph(Surv(time, status) ~ ccr5WM.1 + ccr5WM.2 + strata(trans),
+     data = silong)

Call:
coxph(formula = Surv(time, status) ~ ccr5WM.1 + ccr5WM.2 + strata(trans),
    data = silong)


             coef exp(coef) se(coef)      z        p
ccr5WM.1 -1.2358     0.2906   0.3071 -4.024 5.72e-05
ccr5WM.2 -0.2542     0.7755   0.2380 -1.068    0.286

Likelihood ratio test=23.17  on 2 df, p=9.294e-06
n= 648, number of events= 220
   (10 observations deleted due to missingness)
```

The same model, but now using a covariate by cause interaction.

```
> coxph(Surv(time, status) ~ ccr5 * factor(trans) + strata(trans),
+     data = silong)

Call:
coxph(formula = Surv(time, status) ~ ccr5 * factor(trans) + strata(trans),
    data = silong)


                        coef exp(coef) se(coef)      z        p
ccr5WM                -1.2358     0.2906   0.3071 -4.024 5.72e-05
factor(trans)2             NA        NA   0.0000     NA       NA
ccr5WM:factor(trans)2  0.9816     2.6688   0.3886  2.526   0.0115

Likelihood ratio test=23.17  on 2 df, p=9.294e-06
n= 648, number of events= 220
   (10 observations deleted due to missingness)
```

In the model below we assume that the effect of CCR5 on the two cause-specific hazards is equal. The significant effect of the interaction in the model we just saw indicates that this is not a good idea. But, again, this is just for educational purposes.

```
> coxph(Surv(time, status) ~ ccr5 + strata(trans), data = silong)

Call:
coxph(formula = Surv(time, status) ~ ccr5 + strata(trans), data = silong)
```

```
          coef exp(coef) se(coef)     z        p
ccr5WM -0.7012    0.4960   0.1860 -3.77 0.000163

Likelihood ratio test=16.46  on 1 df, p=4.972e-05
n= 648, number of events= 220
   (10 observations deleted due to missingness)
```

There are two alternative ways yielding the same result. First, we can actually leave out the *strata* term.

```
> coxph(Surv(time, status) ~ ccr5, data = silong)

Call:
coxph(formula = Surv(time, status) ~ ccr5, data = silong)

          coef exp(coef) se(coef)     z        p
ccr5WM -0.7012    0.4960   0.1860 -3.771 0.000163

Likelihood ratio test=16.46  on 1 df, p=4.964e-05
n= 648, number of events= 220
   (10 observations deleted due to missingness)
```

Second, since the *strata* term is not needed we can use si.

```
> coxph(Surv(time, status != 0) ~ ccr5, data = si)

Call:
coxph(formula = Surv(time, status != 0) ~ ccr5, data = si)

          coef exp(coef) se(coef)     z        p
ccr5WM -0.7013    0.4959   0.1860 -3.771 0.000163

Likelihood ratio test=16.47  on 1 df, p=4.953e-05
n= 324, number of events= 220
   (5 observations deleted due to missingness)
```

Note: the actual estimated baseline hazards may be different, whether or not the strata term is used.

Assuming that baseline hazards for AIDS and SI are proportional (this is generally not a realistic assumption by the way, but just for illustration purposes).

```
> coxph(Surv(time, status) ~ ccr5WM.1 + ccr5WM.2 + factor(trans),
+     data = silong)

Call:
coxph(formula = Surv(time, status) ~ ccr5WM.1 + ccr5WM.2 + factor(trans),
    data = silong)

                 coef exp(coef) se(coef)     z        p
ccr5WM.1      -1.1664    0.3115   0.3063 -3.808 0.00014
```

```
ccr5WM.2        -0.3316     0.7178   0.2366 -1.401 0.16112
factor(trans)2 -0.1843     0.8317   0.1477 -1.248 0.21201

Likelihood ratio test=21.54  on 3 df, p=8.124e-05
n= 648, number of events= 220
   (10 observations deleted due to missingness)
```

Or, again using covariate by cause (transition) interaction.

```
> coxph(Surv(time, status) ~ ccr5 * factor(trans), data = silong)

Call:
coxph(formula = Surv(time, status) ~ ccr5 * factor(trans), data = silong)

                       coef exp(coef) se(coef)      z       p
ccr5WM              -1.1664    0.3115   0.3063 -3.808 0.00014
factor(trans)2      -0.1843    0.8317   0.1477 -1.248 0.21201
ccr5WM:factor(trans)2 0.8348    2.3044   0.3855  2.165 0.03035

Likelihood ratio test=21.54  on 3 df, p=8.124e-05
n= 648, number of events= 220
   (10 observations deleted due to missingness)
```

Note that, even though patients are replicated in the long format, it is not necessary to use robust standard errors. Any of the previous analyses with the `silong` dataset gives identical results when a `cluster(id)` term is added. For instance,

```
> coxph(Surv(time, status) ~ ccr5 * factor(trans) + cluster(id),
+      data = silong)

Call:
coxph(formula = Surv(time, status) ~ ccr5 + factor(trans) + ccr5:factor(trans),
    data = silong, cluster = id)

                       coef exp(coef) se(coef) robust se      z       p
ccr5WM              -1.1664    0.3115   0.3063    0.2928 -3.983 6.81e-05
factor(trans)2      -0.1843    0.8317   0.1477    0.1477 -1.248   0.2121
ccr5WM:factor(trans)2 0.8348    2.3044   0.3855    0.3855  2.165   0.0304

Likelihood ratio test=21.54  on 3 df, p=8.124e-05
n= 648, number of events= 220
   (10 observations deleted due to missingness)
```

gives the same result as before.

So far in the regression context we have just used the *coxph* function of the *survival* package. In order to obtain predicted cumulative incidences, *msprep* is useful. First let us store our analysis with separate covariate effects for the two causes.

```
> c1 <- coxph(Surv(time, status) ~ ccr5WM.1 + ccr5WM.2 + strata(trans),
+      data = silong, method = "breslow")
```

If we want the predicted cumulative incidences for an individual with CCR5 wild-type (WW), we make a *newdata* data frame containing the (transition-specific) covariate values for each of the transitions for the individual of interest. Then we apply `msfit` as illustrated earlier in the context of multi-state models.

```
> WW <- data.frame(ccr5WM.1 = c(0, 0), ccr5WM.2 = c(0, 0), trans = c(1,
+     2), strata = c(1, 2))
> msf.WW <- msfit(c1, WW, trans = tmat)
```

And finally, to obtain the cumulative incidences we apply *probtrans*. Item [[1]] is selected because the prediction starts from state 1 (event-free) at time $s = 0$.

```
> pt.WW <- probtrans(msf.WW, 0)[[1]]
```

Similarly for an individual with the CCR5 mutant (WM) genotype.

```
> WM <- data.frame(ccr5WM.1 = c(1, 0), ccr5WM.2 = c(0, 1), trans = c(1,
+     2), strata = c(1, 2))
> msf.WM <- msfit(c1, WM, trans = tmat)
> pt.WM <- probtrans(msf.WM, 0)[[1]]
```

We now plot these cumulative incidence curves for AIDS (`pstate2`) and SI appearance (`pstate3`), for wild-type (WW) and mutant (WM) in Figure 9 (Figure 5 in the tutorial).

```
> idx1 <- (pt.WW$time < 13)
> idx2 <- (pt.WM$time < 13)
> plot(c(0, pt.WW$time[idx1]), c(0, pt.WW$pstate2[idx1]), type = "s",
+     ylim = c(0, 0.5), xlab = "Years from HIV infection", ylab = "Probability",
+     lwd = 2)
> lines(c(0, pt.WM$time[idx2]), c(0, pt.WM$pstate2[idx2]), type = "s",
+     lwd = 2, col = 8)
> title(main = "AIDS")
> text(9.2, 0.345, "WW", adj = 0, cex = 0.75)
> text(9.2, 0.125, "WM", adj = 0, cex = 0.75)
> plot(c(0, pt.WW$time[idx1]), c(0, pt.WW$pstate3[idx1]), type = "s",
+     ylim = c(0, 0.5), xlab = "Years from HIV infection", ylab = "Probability",
+     lwd = 2)
> lines(c(0, pt.WM$time[idx2]), c(0, pt.WM$pstate3[idx2]), type = "s",
+     lwd = 2, col = 8)
> title(main = "SI appearance")
> text(7.5, 0.31, "WW", adj = 0, cex = 0.75)
> text(7.5, 0.245, "WM", adj = 0, cex = 0.75)
```

The illustration of the phenomenon that the same cause-specific hazard ratio may have different effects on the cumulative incidences (Figure 7 in the tutorial) may be performed as well, by replacing the appropriate parts of the cumulative hazard of AIDS (`trans=1`), and calling *probtrans*. We are interested in SI appearance and adjust the hazards of the competing risk (AIDS) while keeping the remainder the same (Figure 7 in the tutorial). The result is shown in Figure 10. We multiply the baseline hazard of AIDS with factors (`ff` = 0, 0.5, 1, 1.5, 2, 4).

```
> ffs <- c(0, 0.5, 1, 1.5, 2, 4)
> newmsf.WW <- msf.WW
> newmsf.WM <- msf.WM
```

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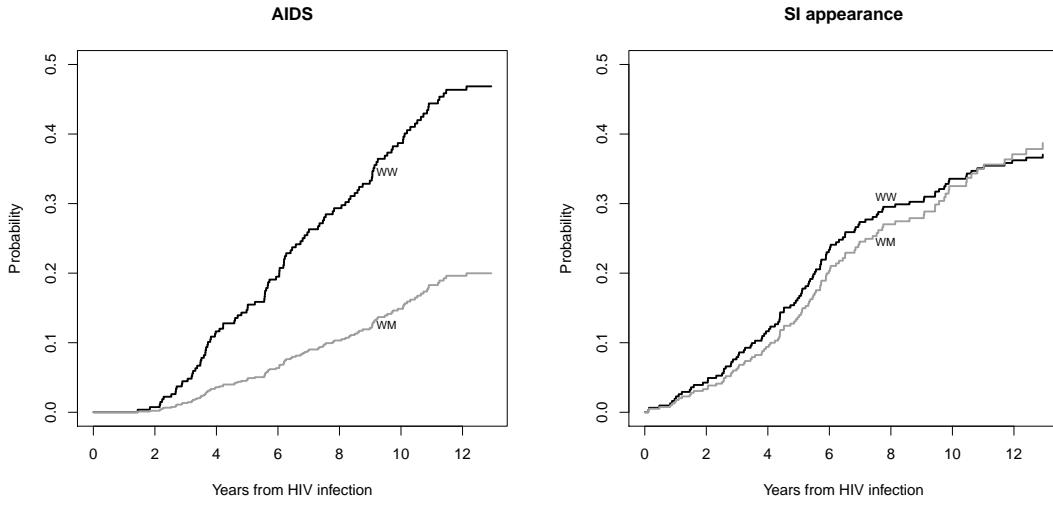
Figure 9: Cumulative incidence functions for AIDS (left) and SI appearance (right), for wild-type (`WW`) and mutant (`WM`) CCR5 genotype, based on a proportional hazards model on the cause-specific hazards.

```
> par(mfrow = c(2, 3))
> for (ff in ffs) {
+     newmsf.WW$Haz$Haz[newmsf.WW$Haz$trans == 1] <- ff * msf.WW$Haz$Haz[msf.WW$Haz$trans ==
+         1]
+     pt.WW <- probtrans(newmsf.WW, 0, variance = FALSE)[[1]]
+     newmsf.WM$Haz$Haz[newmsf.WM$Haz$trans == 1] <- ff * msf.WM$Haz$Haz[msf.WM$Haz$trans ==
+         1]
+     pt.WM <- probtrans(newmsf.WM, 0, variance = FALSE)[[1]]
+     idx1 <- (pt.WW$time < 13)
+     idx2 <- (pt.WM$time < 13)
+     plot(c(0, pt.WW$time[idx1]), c(0, pt.WW$pstate3[idx1]), type = "s",
+         ylim = c(0, 0.52), xlab = "Years from HIV infection",
+         ylab = "Probability", lwd = 2)
+     lines(c(0, pt.WM$time[idx2]), c(0, pt.WM$pstate3[idx2]),
+         type = "s", lwd = 2, col = 8)
+     title(main = paste("Factor =", ff))
+ }
> par(mfrow = c(1, 1))
```

Fine and Gray regression on cumulative incidence functions is not implemented in *mstate*, but in the R package *cmprsk*. Since our main purpose here is illustration of *mstate*, we just give the code and the output.

```
> library(cmprsk)
> sic <- si[!is.na(si$ccr5),]
> ftime <- sic$time
> fstatus <- sic$status
> cov <- as.numeric(sic$ccr5)-1
> # for failures of type 1 (AIDS)
> z1 <- crr(ftime,fstatus,cov)
```
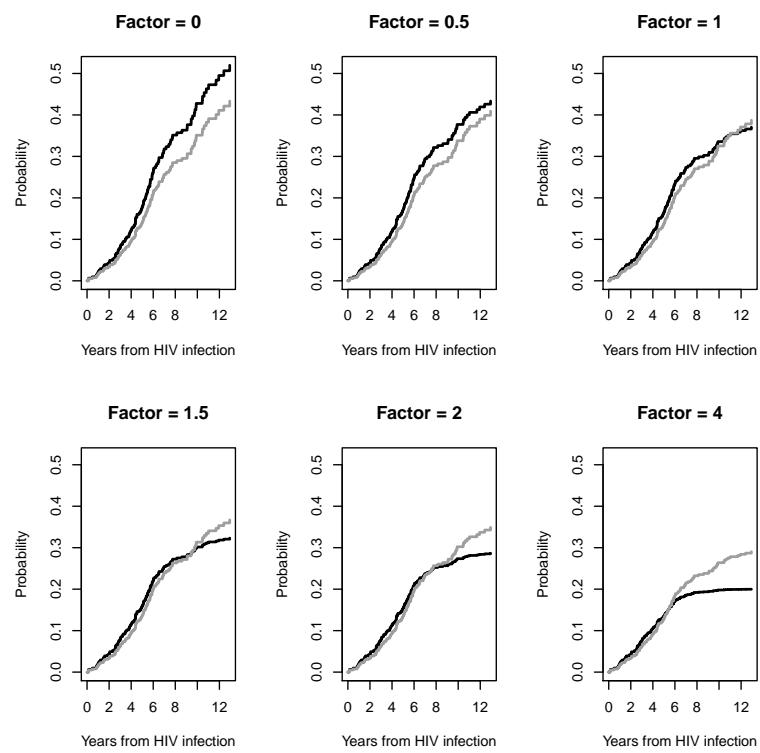
Figure 10: Cumulative incidence functions for Si appearance, for CCR5 wild-type `WW` (black) and mutant `WM` (grey). The baseline hazard of AIDS was multiplied with different factors, while keeping everything else the same.

```
> z1

convergence:   TRUE
coefficients:
  cov1
-1.004
standard errors:
[1] 0.295
two-sided p-values:
   cov1
0.00066

> # for failures of type 2 (SI)
> z2 <- crr(ftime,fstatus,cov,failcode=2)
> z2

convergence:   TRUE
coefficients:
   cov1
0.02359
standard errors:
[1] 0.2266
two-sided p-values:
cov1
0.92
```

The result (Figure 8 in the tutorial) is shown in Figure 11.

```
> z1.pr <- predict(z1,matrix(c(0,1),2,1))
> # this will contain predicted cum inc curves, both for WW (2nd column) and WM (3rd)
> z2.pr <- predict(z2,matrix(c(0,1),2,1))
> # Standard plots, not shown
> par(mfrow=c(1,2))
> plot(z1.pr,lty=1,lwd=2,color=c(8,1))
> plot(z2.pr,lty=1,lwd=2,color=c(8,1))
> par(mfrow=c(1,1))
> ## AIDS
> n1 <- nrow(z1.pr) # remove last jump
> plot(c(0,z1.pr[-n1,1]),c(0,z1.pr[-n1,2]),type="s",ylim=c(0,0.5),
+     xlab="Years from HIV infection",ylab="Probability",lwd=2)
> lines(c(0,z1.pr[-n1,1]),c(0,z1.pr[-n1,3]),type="s",lwd=2,col=8)
> title(main="AIDS")
> text(9.3,0.35,"WW",adj=0,cex=0.75)
> text(9.3,0.14,"WM",adj=0,cex=0.75)
> ## SI appearance
> n2 <- nrow(z2.pr) # again remove last jump
> plot(c(0,z2.pr[-n2,1]),c(0,z2.pr[-n2,2]),type="s",ylim=c(0,0.5),
+     xlab="Years from HIV infection",ylab="Probability",lwd=2)
> lines(c(0,z2.pr[-n2,1]),c(0,z2.pr[-n2,3]),type="s",lwd=2,col=8)
> title(main="SI appearance")
> text(7.9,0.28,"WW",adj=0,cex=0.75)
> text(7.9,0.31,"WM",adj=0,cex=0.75)
```
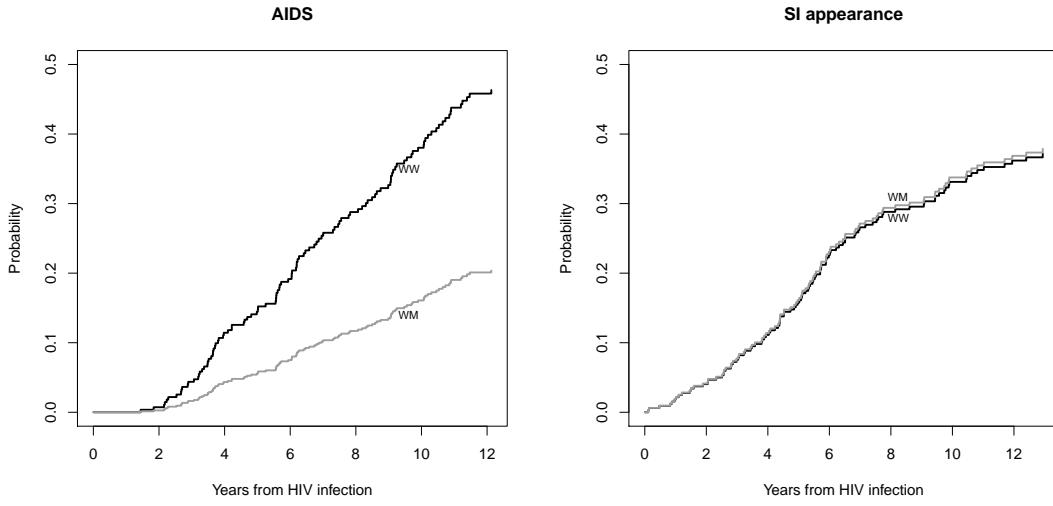
Figure 11: Cumulative incidence functions for AIDS (left) and SI appearance (right), for CCR5 wild-type `WW` and mutant `WM`, based on the Fine and Gray model.

To judge the "fit" of the cause-specific and Fine & Gray regression models we estimate cumulative incidence curves nonparametrically, i.e., for two subgroups of WW and WM CCR5-genotypes. Here we can use the *group* argument of `Cuminc`.

```
> ci <- Cuminc(si$time, si$status, group = si$ccr5)
> ci.WW <- ci[ci$group == "WW", ]
> ci.WM <- ci[ci$group == "WM", ]
```

We show these nonparametric estimates in Figure 12 (Figure 9 in the tutorial).

```
> idx1 <- (ci.WW$time < 13)
> idx2 <- (ci.WM$time < 13)
> plot(c(0, ci.WW$time[idx1]), c(0, ci.WW$CI.1[idx1]), type = "s",
+     ylim = c(0, 0.5), xlab = "Years from HIV infection", ylab = "Probability",
+     lwd = 2)
> lines(c(0, ci.WM$time[idx2]), c(0, ci.WM$CI.1[idx2]), type = "s",
+     lwd = 2, col = 8)
> title(main = "AIDS")
> text(9.3, 0.35, "WW", adj = 0, cex = 0.75)
> text(9.3, 0.11, "WM", adj = 0, cex = 0.75)
> plot(c(0, ci.WW$time[idx1]), c(0, ci.WW$CI.2[idx1]), type = "s",
+     ylim = c(0, 0.5), xlab = "Years from HIV infection", ylab = "Probability",
+     lwd = 2)
> lines(c(0, ci.WM$time[idx2]), c(0, ci.WM$CI.2[idx2]), type = "s",
+     lwd = 2, col = 8)
> title(main = "SI appearance")
> text(7.9, 0.32, "WW", adj = 0, cex = 0.75)
> text(7.9, 0.245, "WM", adj = 0, cex = 0.75)
```

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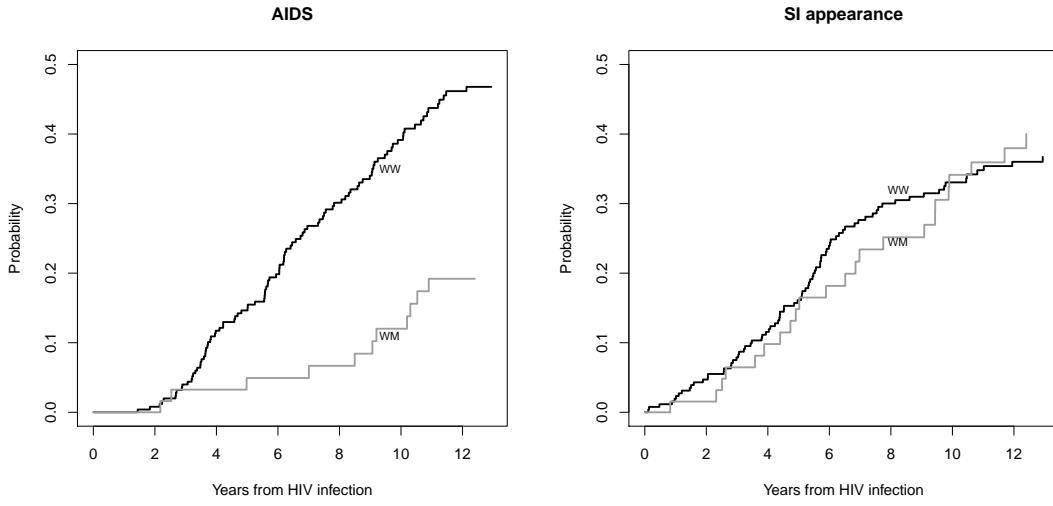
Figure 12: Non-parametric cumulative incidence functions for AIDS (left) and SI appearance (right), for CCR5 wild-type `WW` and mutant `WM`.

References

Andersen, P. K., Borgan, Ø., Gill, R. D. & Keiding, N. (1993), *Statistical Models Based on Counting Processes*, Springer-Verlag.

de Wreede, L., Fiocco, M. & Putter, H. (2009), 'The mstate package for estimation and prediction in non- and semi-parametric multi-state models'. Submitted.

Putter, H., Fiocco, M. & Geskus, R. B. (2007), 'Tutorial in biostatistics: Competing risks and multi-state models', *Statist Med* **26**, 2389–2430.