Missing values and modelling in R

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February 3, 2016

1 Introduction

In class today, we were working with the lung cancer data set from the `survival` package. This had some missing data in it:

```
library(survival)
head(lung,10)

##    inst time status age sex ph.ecog ph.karno pat.karno meal.cal wt.loss
## 1     3  306      2  74   1       1       90       100     1175      NA
## 2     3  455      2  68   1       0       90        90     1225      15
## 3     3 1010      1  56   1       0       90        90       NA      15
## 4     5  210      2  57   1       1       90        60     1150      11
## 5     1  883      2  60   1       0      100        90       NA       0
## 6    12 1022      1  74   1       1       50        80      513       0
## 7     7  310      2  68   2       2       70        60      384      10
## 8    11  361      2  71   2       2       60        80      538       1
## 9     1  218      2  53   1       1       70        80      825      16
## 10    7  166      2  61   1       2       70        70      271      34
```

You might have been wondering why (a) I could fit models, but (b) why I could *not* do `anova` and suchlike things (which I really ought to have done, from a data analysis point of view.)

2 Complete cases

An observation (row) of the data frame that has values for all the variables is called a **complete case**. Or, if there are any missing values anywhere along the row, it is *not* a complete case.

In the lung cancer data frame excerpt above, rows 1, 3 and 5 have missing values in them somewhere, but the other rows are all complete cases.

R has a function called `complete.cases` that takes a data frame and returns `TRUE` if that row is a complete case and `FALSE` if it has any missing values anywhere. Here is the output from running `complete.cases` on the first 10 rows of our data frame:

```
v=complete.cases(lung)
v[1:10]

##  [1] FALSE  TRUE FALSE  TRUE FALSE  TRUE  TRUE  TRUE  TRUE  TRUE
```

Or, more precisely, of running it on the whole data frame and showing you the first ten values. Values 1, 3 and 5 are `FALSE`, corresponding to those rows having missing values in them somewhere, and the other values are `TRUE`, meaning that those rows are complete cases with no missing values.

When we fit a model, only the relevantly complete cases are used (I expand on this in a moment). The simplest situation is if the model has all the explanatory variables in it, like this:

```
attach(lung)
resp=Surv(time,status==2)
lung.1=coxph(resp~age+sex+ph.ecog+ph.karno+pat.karno+
  meal.cal+wt.loss)
summary(lung.1)

## Call:
## coxph(formula = resp ~ age + sex + ph.ecog + ph.karno + pat.karno +
##     meal.cal + wt.loss)
##
##   n= 168, number of events= 121
##    (60 observations deleted due to missingness)
##
##                  coef  exp(coef)   se(coef)      z Pr(>|z|)
## age        1.065e-02  1.011e+00  1.161e-02  0.917  0.35906
## sex       -5.509e-01  5.765e-01  2.008e-01 -2.743  0.00609 **
## ph.ecog    7.342e-01  2.084e+00  2.233e-01  3.288  0.00101 **
## ph.karno   2.246e-02  1.023e+00  1.124e-02  1.998  0.04574 *
## pat.karno -1.242e-02  9.877e-01  8.054e-03 -1.542  0.12316
## meal.cal   3.329e-05  1.000e+00  2.595e-04  0.128  0.89791
## wt.loss   -1.433e-02  9.858e-01  7.771e-03 -1.844  0.06518 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##           exp(coef) exp(-coef) lower .95 upper .95
## age          1.0107     0.9894    0.9880    1.0340
## sex          0.5765     1.7347    0.3889    0.8545
## ph.ecog      2.0838     0.4799    1.3452    3.2277
## ph.karno     1.0227     0.9778    1.0004    1.0455
## pat.karno    0.9877     1.0125    0.9722    1.0034
## meal.cal     1.0000     1.0000    0.9995    1.0005
## wt.loss      0.9858     1.0144    0.9709    1.0009
##
```

```
## Concordance= 0.651  (se = 0.031 )
## Rsquare= 0.155   (max possible= 0.998 )
## Likelihood ratio test= 28.33  on 7 df,   p=0.0001918
## Wald test            = 27.58  on 7 df,   p=0.0002616
## Score (logrank) test = 28.41  on 7 df,   p=0.0001849
```

This uses 168 observations (as the output shows). This is how many complete cases there are:

```
table(v)

## v
## FALSE  TRUE
##    61   167
```

Oh, not quite the same. But I can explain that too. I explain that in a minute, but this is relevant in the meanwhile:

```
summary(lung)

##       inst            time            status           age
##  Min.   : 1.00   Min.   :   5.0   Min.   :1.000   Min.   :39.00
##  1st Qu.: 3.00   1st Qu.: 166.8   1st Qu.:1.000   1st Qu.:56.00
##  Median :11.00   Median : 255.5   Median :2.000   Median :63.00
##  Mean   :11.09   Mean   : 305.2   Mean   :1.724   Mean   :62.45
##  3rd Qu.:16.00   3rd Qu.: 396.5   3rd Qu.:2.000   3rd Qu.:69.00
##  Max.   :33.00   Max.   :1022.0   Max.   :2.000   Max.   :82.00
##  NA's   :1
##       sex           ph.ecog          ph.karno        pat.karno
##  Min.   :1.000   Min.   :0.0000   Min.   : 50.00   Min.   : 30.00
##  1st Qu.:1.000   1st Qu.:0.0000   1st Qu.: 75.00   1st Qu.: 70.00
##  Median :1.000   Median :1.0000   Median : 80.00   Median : 80.00
##  Mean   :1.395   Mean   :0.9515   Mean   : 81.94   Mean   : 79.96
##  3rd Qu.:2.000   3rd Qu.:1.0000   3rd Qu.: 90.00   3rd Qu.: 90.00
##  Max.   :2.000   Max.   :3.0000   Max.   :100.00   Max.   :100.00
##                  NA's   :1        NA's   :1        NA's   :3
##     meal.cal         wt.loss
##  Min.   :  96.0   Min.   :-24.000
##  1st Qu.: 635.0   1st Qu.:  0.000
##  Median : 975.0   Median :  7.000
##  Mean   : 928.8   Mean   :  9.832
##  3rd Qu.:1150.0   3rd Qu.: 15.750
##  Max.   :2600.0   Max.   : 68.000
##  NA's   :47       NA's   :14
```

Now, suppose I decide to take out `meal.cal` since that is nowhere near significant. I could go blindly like this, and wonder what happened:

```
lung.2=coxph(resp~age+sex+ph.ecog+ph.karno+pat.karno+wt.loss)
anova(lung.2,lung.1)

## Error in anova.coxphlist(c(list(object), dotargs), test = test):
models were not all fitted to the same size of dataset
```

The answer to this riddle is found by looking at the `summary` of our smaller model:

```
summary(lung.2)

## Call:
## coxph(formula = resp ~ age + sex + ph.ecog + ph.karno + pat.karno +
##     wt.loss)
##
##   n= 210, number of events= 148
##    (18 observations deleted due to missingness)
##
##                 coef exp(coef)  se(coef)      z Pr(>|z|)
## age         0.013058  1.013144  0.009866  1.324 0.185639
## sex        -0.625167  0.535172  0.178703 -3.498 0.000468 ***
## ph.ecog     0.675227  1.964479  0.198735  3.398 0.000680 ***
## ph.karno    0.020116  1.020320  0.010178  1.976 0.048111 *
## pat.karno -0.014743  0.985365  0.007300 -2.019 0.043440 *
## wt.loss    -0.013243  0.986844  0.007009 -1.889 0.058836 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##           exp(coef) exp(-coef) lower .95 upper .95
## age          1.0131     0.9870    0.9937    1.0329
## sex          0.5352     1.8686    0.3770    0.7596
## ph.ecog      1.9645     0.5090    1.3307    2.9001
## ph.karno     1.0203     0.9801    1.0002    1.0409
## pat.karno    0.9854     1.0149    0.9714    0.9996
## wt.loss      0.9868     1.0133    0.9734    1.0005
##
## Concordance= 0.656  (se = 0.028 )
## Rsquare= 0.162   (max possible= 0.998 )
## Likelihood ratio test= 37.2  on 6 df,   p=1.611e-06
## Wald test            = 36.49  on 6 df,   p=2.209e-06
## Score (logrank) test = 37.59  on 6 df,   p=1.352e-06
```

The model `lung.2` without `meal.cal` is based on 210 observations, much more than the 168 observations on which `lung.1` was based. We can't very well compare two models fit to different data, and indeed `anova` won't let us do that (that was the error message).

Why the big difference? Let's look at the top of the data frame again:

```
head(lung)
```

```
##   inst time status age sex ph.ecog ph.karno pat.karno meal.cal wt.loss
## 1    3  306      2  74   1       1       90       100     1175      NA
## 2    3  455      2  68   1       0       90        90     1225      15
## 3    3 1010      1  56   1       0       90        90       NA      15
## 4    5  210      2  57   1       1       90        60     1150      11
## 5    1  883      2  60   1       0      100        90       NA       0
## 6   12 1022      1  74   1       1       50        80      513       0
```

Take a look at rows 3 and 5. These observations are missing `meal.cal` but nothing else. So, as far as a model without `meal.cal` is concerned, these are now complete cases, because they have values for all the variables that feature in the model. That is what I meant by "relevantly complete": rows 3 and 5 (and evidently a lot of others) are complete cases as far as `lung.2` is concerned, which is why `lung.2` is based on a lot more observations than `lung.1`. If you look at the output to `summary(lung)` above (the summary of the data frame), you'll see that `meal.cal` has 47 missing observations. Some of these (though probably not many) are going to have other missing values as well (and therefore aren't in `lung.2` either), but most of them will have the `meal.cal` as the only missing value, and therefore they will be included in `lung.2` but not in `lung.1`.

So why did I have 168 observations in `lung.1` but only 167 complete cases? "Relevantly complete" is the answer here too. One observation has a missing value for `inst` but is otherwise complete. Since `inst` didn't feature in `lung.1`, this observation is a complete case for `lung.1`.

This all explains my rather cavalier treatment of model-building in class. The only other way I could go is to deliberately remove the one least significant explanatory variable at a time, and that would have taken too long in class.

3 Using only the complete cases

The other option is to throw out all the observations with any missing values before you start. That way, you know that all your analyses are based on the same data set, and the issue of "relevantly complete" is, um, irrelevant. If you do that, you might lose a lot of data off the top, but you have all the apparatus of model-building available to you.

How to keep only the complete cases? Remember the function `complete.cases`? That was `TRUE` if the row was complete and `FALSE` if it had any missing values. We can use that to select only the rows without missings like this:

```
v=complete.cases(lung)
lung.nom=lung[v,]
head(lung.nom)
```

```
##   inst time status age sex ph.ecog ph.karno pat.karno meal.cal wt.loss
## 2    3  455      2  68   1       0       90        90     1225      15
## 4    5  210      2  57   1       1       90        60     1150      11
## 6   12 1022      1  74   1       1       50        80      513       0
## 7    7  310      2  68   2       2       70        60      384      10
## 8   11  361      2  71   2       2       60        80      538       1
## 9    1  218      2  53   1       1       70        80      825      16
```

No missing values here (or, presumably, anywhere else in `lung.nom`). Note that the row numbers come from the *original* data frame, rows 1, 3 and 5 of which must have had (and did have) missing values. `lung.nom` ought to have 167 rows, since that's how many completely complete cases we had:

```
dim(lung.nom)

## [1] 167  10
```

If you like `dplyr`, you can also pull out the complete cases that way. The smartest thing is to save the result of `complete.cases` *inside* the data frame:

```
library(dplyr)

##
## Attaching package:  'dplyr'
## The following objects are masked from 'package:stats':
##
##     filter, lag
## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union

lung %>% mutate(comp=complete.cases(lung)) %>% filter(comp) -> lung.nom
dim(lung.nom)

## [1] 167  11
```

The extra column is that `comp` I created, which will be completely `TRUE` in `lung.nom`.

4 Modelling with the complete cases

If we use the data frame `lung.nom` with no missing values, we have all the modelling machinery available to us. But we have to go back and start again:

```
detach(lung)
attach(lung.nom)
y=Surv(time,status==2)
lung.nom.1=coxph(y~age+sex+ph.ecog+ph.karno+pat.karno+meal.cal+wt.loss)
lung.nom.2=update(lung.nom.1,.~.-meal.cal)
anova(lung.nom.2,lung.nom.1)

## Analysis of Deviance Table
##  Cox model: response is  y
##  Model 1: ~ age + sex + ph.ecog + ph.karno + pat.karno + wt.loss
##  Model 2: ~ age + sex + ph.ecog + ph.karno + pat.karno + meal.cal + wt.loss
##    loglik  Chisq Df P(>|Chi|)
## 1 -494.04
## 2 -494.03 0.0119  1    0.9132
```

We can also use `drop1` to help us decide what should come out next:

```
drop1(lung.nom.2,test="Chisq")

## Single term deletions
##
## Model:
## y ~ age + sex + ph.ecog + ph.karno + pat.karno + wt.loss
##           Df     AIC     LRT  Pr(>Chi)
## <none>       1000.08
## age        1  998.95  0.8714 0.3505744
## sex        1 1006.29  8.2053 0.0041769 **
## ph.ecog    1 1009.09 11.0138 0.0009043 ***
## ph.karno   1 1002.28  4.2018 0.0403808 *
## pat.karno  1 1000.29  2.2073 0.1373553
## wt.loss    1 1001.60  3.5196 0.0606477 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

It appears to be `age`.

And if you are lazy (or efficient, depending on your point of view), you can do the whole elimination in one go:

```
step(lung.nom.1)

## Start:  AIC=1002.07
## y ~ age + sex + ph.ecog + ph.karno + pat.karno + meal.cal + wt.loss
##
##             Df    AIC
## - meal.cal   1 1000.1
## - age        1 1001.0
## <none>         1002.1
## - pat.karno  1 1002.3
## - wt.loss    1 1003.6
## - ph.karno   1 1004.3
## - sex        1 1008.0
## - ph.ecog    1 1011.1
##
## Step:  AIC=1000.08
## y ~ age + sex + ph.ecog + ph.karno + pat.karno + wt.loss
##
##             Df     AIC
## - age        1  998.95
## <none>         1000.08
## - pat.karno  1 1000.29
## - wt.loss    1 1001.60
## - ph.karno   1 1002.28
## - sex        1 1006.29
## - ph.ecog    1 1009.09
##
## Step:  AIC=998.95
## y ~ sex + ph.ecog + ph.karno + pat.karno + wt.loss
##
##             Df     AIC
## <none>          998.95
## - pat.karno  1  999.34
## - ph.karno   1 1000.53
## - wt.loss    1 1000.74
## - sex        1 1005.25
## - ph.ecog    1 1007.83
## Call:
## coxph(formula = y ~ sex + ph.ecog + ph.karno + pat.karno + wt.loss)
##
##
##               coef exp(coef) se(coef)     z      p
## sex       -0.55819   0.57224  0.19920 -2.80 0.0051
## ph.ecog    0.74298   2.10220  0.22760  3.26 0.0011
## ph.karno   0.02037   1.02057  0.01108  1.84 0.0660
## pat.karno -0.01240   0.98768  0.00798 -1.55 0.1201
## wt.loss   -0.01449   0.98561  0.00769 -1.88 0.0596
##
## Likelihood ratio test=27.3  on 5 df, p=5.03e-05
## n= 167, number of events= 120
```

Following the process through, we eliminate `meal.cal` and then age, but stop there, leaving everything else in the model.

This is based on AIC rather than tests, so it can leave some tangentially relevant variables in the model.

I think we should now go back and fit this model to the whole data set, so that we can take advantage of the relevantly-complete cases:

```
detach(lung.nom)
lung.4=coxph(resp~sex+ph.ecog+ph.karno+pat.karno+wt.loss,data=lung)
summary(lung.4)

## Call:
## coxph(formula = resp ~ sex + ph.ecog + ph.karno + pat.karno +
##     wt.loss, data = lung)
##
##   n= 210, number of events= 148
##    (18 observations deleted due to missingness)
##
##                coef exp(coef)  se(coef)      z Pr(>|z|)
## sex       -0.614915  0.540687  0.177886 -3.457 0.000547 ***
## ph.ecog    0.682441  1.978702  0.201278  3.391 0.000698 ***
## ph.karno   0.018887  1.019066  0.010267  1.840 0.065838 .
## pat.karno -0.015255  0.984861  0.007306 -2.088 0.036797 *
## wt.loss   -0.012914  0.987169  0.006844 -1.887 0.059162 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##           exp(coef) exp(-coef) lower .95 upper .95
## sex          0.5407     1.8495    0.3815    0.7662
## ph.ecog      1.9787     0.5054    1.3337    2.9357
## ph.karno     1.0191     0.9813    0.9988    1.0398
## pat.karno    0.9849     1.0154    0.9709    0.9991
## wt.loss      0.9872     1.0130    0.9740    1.0005
##
## Concordance= 0.659  (se = 0.028 )
## Rsquare= 0.155   (max possible= 0.998 )
## Likelihood ratio test= 35.41  on 5 df,   p=1.245e-06
## Wald test            = 35.47  on 5 df,   p=1.214e-06
## Score (logrank) test = 36.33  on 5 df,   p=8.158e-07
```

We had to be careful to use the response variable `resp` that came from the *original* data set, not the new one `y` that we created from only the complete cases.

The result from `step` and the model `lung.4` won't be exactly the same, because they are based on different data, but the overall picture should be similar. In each case here, the two Karnofsky scores and weight loss were teetering on the brink of significance.

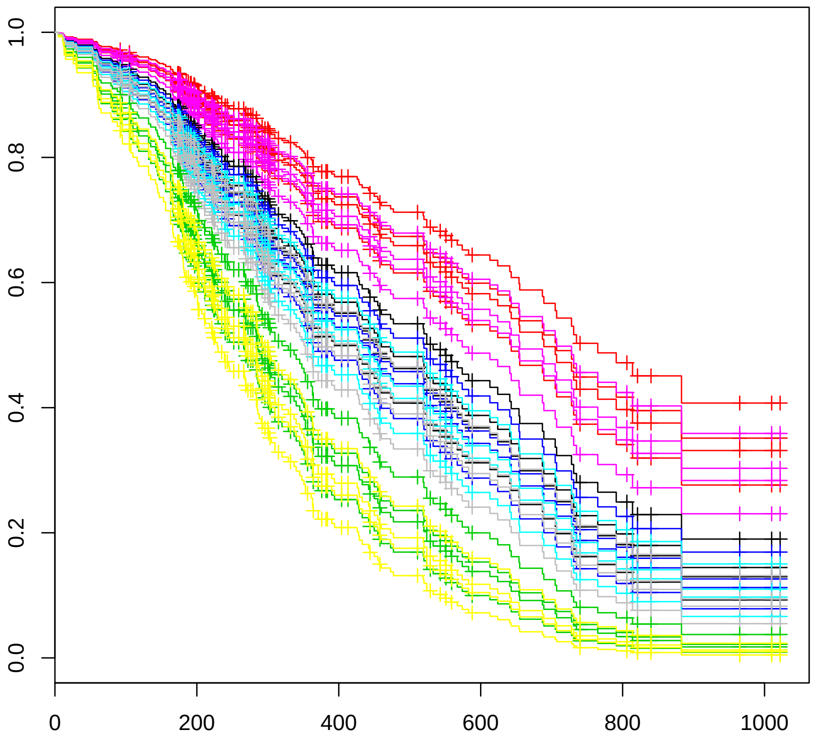
Also, predictions from `lung.4` ought to be better because they are based on more data.

Talking of predictions, how can we do predictions with so many variables? I think we have to distinguish them by colours:

```
sexes=c(1,2)
ph.ecogs=c(0,1)
ph.karnos=c(75,82)
pat.karnos=c(70,80)
wt.losses=c(0,16)
```

We have so many variables, so I only picked two values (the quartiles) for each, to stop the "newdata" data frame from getting too big. As it is, it'll have $2^5 = 32$ rows, which is going to make for a very busy plot.

```
new=expand.grid(sex=sexes,ph.ecog=ph.ecogs,ph.karno=ph.karnos,
  pat.karno=pat.karnos,wt.loss=wt.losses)
pp=survfit(lung.4,new)
plot(pp,col=1:32)
```



Pretty, but very uninformative (there are too many colours to tell apart). I can't even imagine getting a 32-item legend on there.

Or we go back to the summary of `lung.4`:

```
summary(lung.4)$coefficients

##                   coef exp(coef)    se(coef)         z     Pr(>|z|)
## sex        -0.61491517 0.5406868 0.177885551 -3.456802 0.0005466258
## ph.ecog     0.68244129 1.9787024 0.201278422  3.390534 0.0006975666
## ph.karno    0.01888670 1.0190662 0.010267173  1.839522 0.0658383733
## pat.karno  -0.01525472 0.9848610 0.007305883 -2.088005 0.0367973944
## wt.loss    -0.01291366 0.9871694 0.006843528 -1.886988 0.0591619075
```

What is associated with survival (not dying) is a higher value of **`sex`** (being female), a lower value of **`ph.ecog`** (which makes sense), a lower value of **`ph.karno`** (which makes no sense since higher is supposed to be better), a higher value of **`pat.karno`**, as expected, and oddly a *higher* value of **`wt.loss`**.

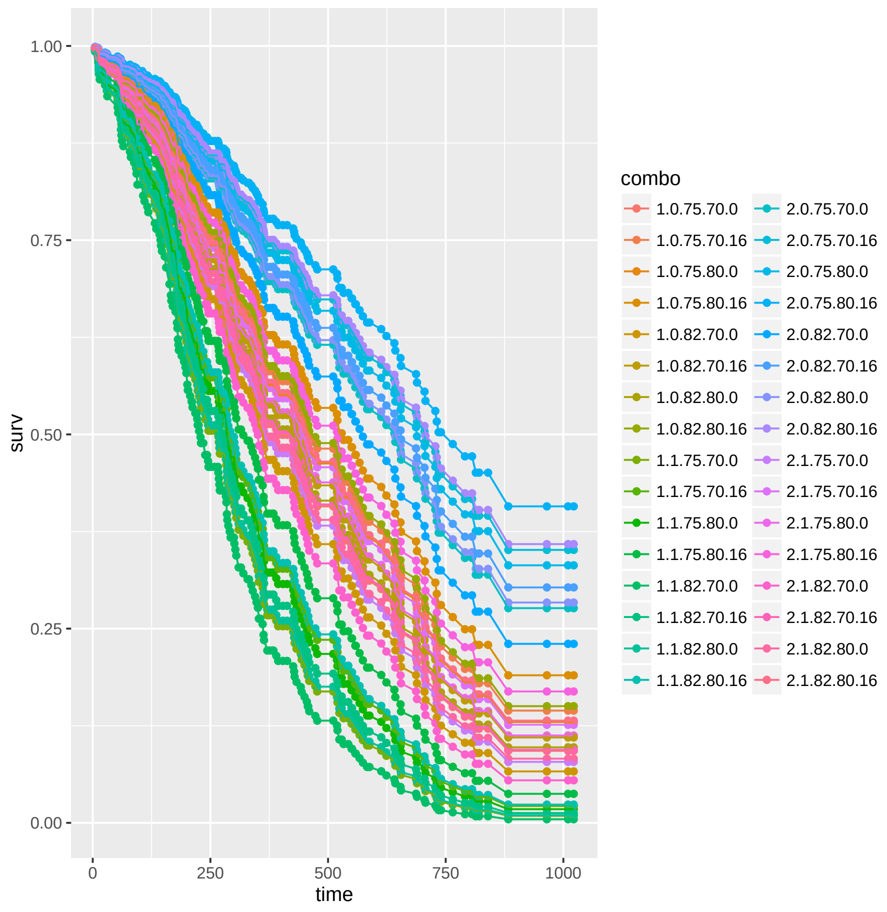
Am I brave enough to try to do this in **`ggplot`**? I'm going to use my function **`ggsurvplot`**[1] from my solutions to assignment 4 (question 5; see there for what this function does):

```
ggsurvplot=function(s,new) {
  # s is output from survfit
  # new is combos of values that were predicted for
  newnames=do.call(paste, c(new, sep="."))
  v=data.frame(time=s$time,surv=s$surv)
  names(v)=c("time",newnames)
  p=gather(v,combo,surv,-time)
  ggplot(p,aes(x=time,y=surv,colour=combo))+
    geom_point()+geom_line()
}
```

and then run it:

```
library(tidyr)
library(ggplot2)
ggsurvplot(pp,new)
```

[1]One of the first things you learn as a programmer is to re-use what you did before rather than reinventing the wheel.



Good luck picking out the colour of the best combination! The labels on the legend are the values of the five variables in the order that we put them in `new` (that is, the same order as in the `expand.grid`). I think the best one ought to be `2.0.75.80.16` (those are respectively high, low, low, high, high of the values we chose for those five variables). Which is certainly one of those blue ones, but I'm not sure whether it's *that* one.

Qualitatively, the best survival curves are the blue and purple ones (females with the best ECOG score of zero), and the worst ones are the green ones (males with the worse ECOG score of 1). The better-ECOG males (orange) and the worse-ECOG females (pink) are all mixed up in the middle.