Weibull Regression with R, Part One*

Comparing Two Treatments

The Pharmaco-smoking study

The purpose of this study ... was to evaluate extended duration of a triple-medication combination versus therapy with the nicotine patch alone in smokers with medical illnesses. Patients with a history of smoking were randomly assigned to the triple-combination or patch therapy and followed for up to six months. The primary outcome variable was time from randomization until relapse (return to smoking); individuals who remained non-smokers for six months were censored. The data set, “pharmacoSmoking”, is available in the “asaur” package.

The variable “ttr” is the number of days without smoking (“time to relapse”), and “relapse=1” indicates that the subject started smoking again at the given time. The variable “grp” is the treatment indicator, and “employment” can take the values “ft” (full time), “pt” (part time), or “other”.
This material is quoted from *Applied Survival Analysis Using R*, pages 18-19.

```
> rm(list=ls()); # options(scipen=999)
> # install.packages("survival",dependencies=TRUE) # Only need to do this once
> library(survival) # Do this every time
> # install.packages("asaur",dependencies=TRUE) # Only need to do this once
> library(asaur)
> # help(pharmacoSmoking)
```

```
> head(pharmacoSmoking)
   id ttr relapse         grp age gender     race employment yearsSmoking
1  21 182       0   patchOnly  36   Male    white         ft           26
2 113  14       1   patchOnly  41   Male    white      other           27
3  39   5       1 combination  25 Female    white      other           12
4  80  16       1 combination  54   Male    white         ft           39
5  87   0       1 combination  45   Male    white      other           30
6  29 182       0 combination  43   Male hispanic         ft           30
  levelSmoking ageGroup2 ageGroup4 priorAttempts longestNoSmoke
1        heavy     21-49     35-49             0              0
2        heavy     21-49     35-49             3             90
3        heavy     21-49     21-34             3             21
4        heavy       50+     50-64             0              0
5        heavy     21-49     35-49             0              0
6        heavy     21-49     35-49             2           1825
> summary(pharmacoSmoking)
       id              ttr             relapse                grp          age
 Min.   :  1.00   Min.   :  0.00   Min.   :0.000   combination:61   Min.   :22.00
 1st Qu.: 33.00   1st Qu.:  8.00   1st Qu.:0.000   patchOnly  :64   1st Qu.:41.00
 Median : 67.00   Median : 49.00   Median :1.000                    Median :49.00
 Mean   : 66.15   Mean   : 77.44   Mean   :0.712                    Mean   :48.84
 3rd Qu.: 99.00   3rd Qu.:182.00   3rd Qu.:1.000                    3rd Qu.:56.00
 Max.   :130.00   Max.   :182.00   Max.   :1.000                    Max.   :86.00
    gender          race     employment  yearsSmoking   levelSmoking ageGroup2
 Female:81   black   :38   ft   :72    Min.   : 9.00   heavy:89     21-49:66
 Male  :44   hispanic: 8   other:39    1st Qu.:22.00   light:36     50+  :59
             other   : 2   pt   :14    Median :30.00
             white   :77               Mean   :30.88
                                       3rd Qu.:39.00
                                       Max.   :56.00
 ageGroup4  priorAttempts      longestNoSmoke
 21-34:16   Min.   :   0.00   Min.   :   0.0
 35-49:50   1st Qu.:   1.00   1st Qu.:   7.0
 50-64:48   Median :   2.00   Median :  90.0
 65+  :11   Mean   :  12.68   Mean   : 539.7
            3rd Qu.:   5.00   3rd Qu.: 365.0
            Max.   :1000.00   Max.   :6205.0
> quit = within(pharmacoSmoking, {TimeToRelapse = Surv(ttr,relapse)} )
> sort(quit$TimeToRelapse)
  [1]    0    0    0    0    0    0    0    0    0    0    0    0    1    1    1
 [16]    1    1    2    2    2    2    2    2    3    4    4    4    5    5    6
 [31]    7    8    8    8   10   12   12   14   14   14   14   14   14   14   15
 [46]   15   15   15   16   20   21   21   25   28   28   28   30   30   30   40
 [61]   42   45   49   50   56   56   56   56   56   60   60   63   63   65   75
 [76]   77   77   80   84  100  105  110  140  140  140  140  155  170  170 182+
 [91] 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+
[106] 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+ 182+
[121] 182+ 182+ 182+ 182+ 182+
```

```
> # Fit a Weibull model with just treatment group, which was randomly assigned.
> Model0 = survreg(TimeToRelapse~grp,dist='weibull', data=quit)
Error in survreg(TimeToRelapse ~ grp, dist = "weibull", data = quit) :
  Invalid survival times for this distribution
> # Likely choking on the zeros.
> # Day of relapse starts with one.
> quit = within(quit, {DayOfRelapse = Surv(ttr+1,relapse)} )
> Model0 = survreg(DayOfRelapse~grp,dist='weibull', data=quit)
> summary(Model0)


Call:
survreg(formula = DayOfRelapse ~ grp, dist = "weibull")
              Value Std. Error     z        p
(Intercept)   5.260     0.3053 17.23 1.60e-66
grppatchOnly -1.162     0.3999 -2.91 3.67e-03
Log(scale)    0.606     0.0904  6.70 2.14e-11

Scale= 1.83

Weibull distribution
Loglik(model)= -472.1   Loglik(intercept only)= -476.5
      Chisq= 8.78 on 1 degrees of freedom, p= 0.003
Number of Newton-Raphson Iterations: 5
n= 125
```

Conclusion is that combination therapy is more effective. But the alphabetical order of treatments makes combination the reference category, and this is clumsy. Make patch-only the reference category and re-run. This is what we have.

Treatment	d	$E(Y\|\mathbf{X}=\mathbf{x}) = \beta_0 + \beta_1 d$
Combination	0	β_0
Patch Only	1	$\beta_0 + \beta_1$

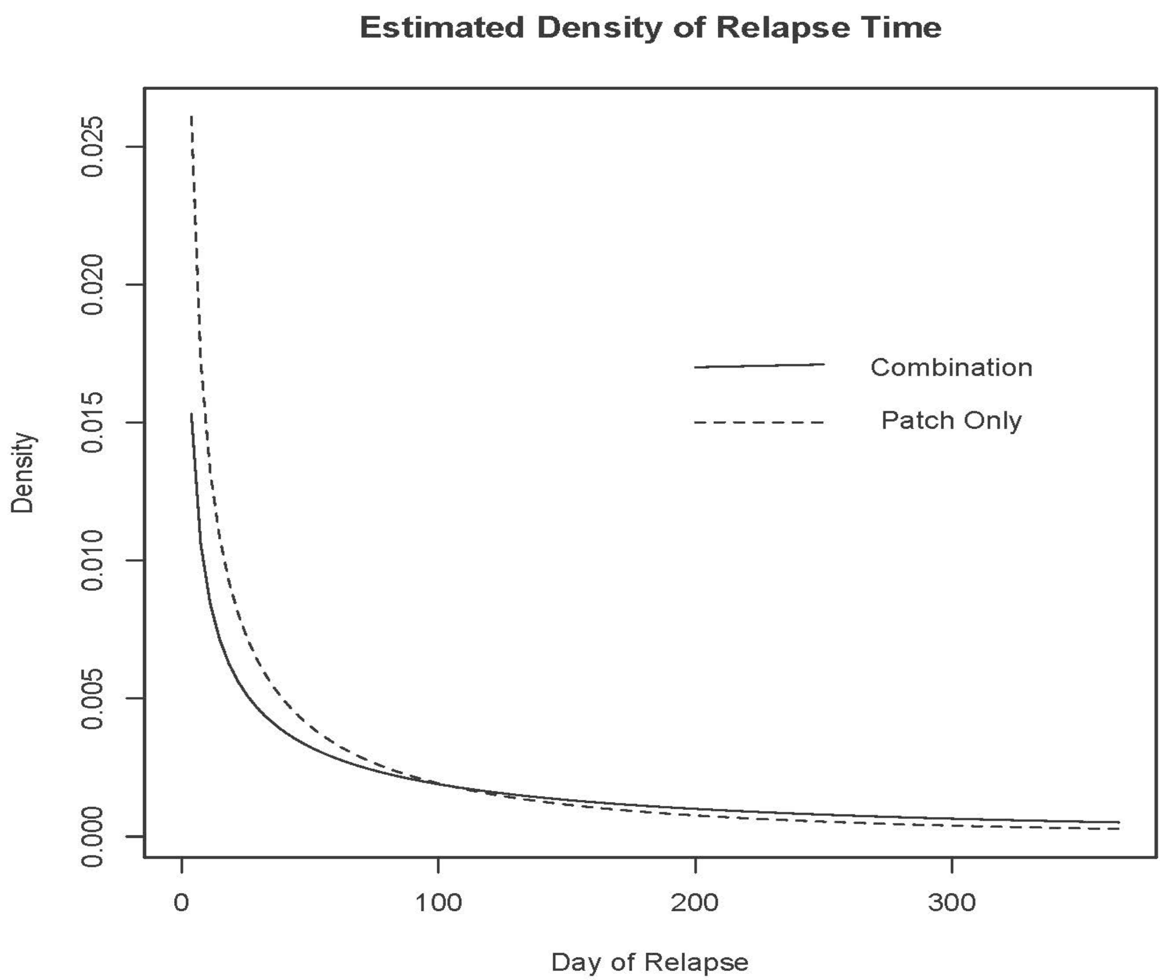
This is what we want.

Treatment	d	$E(Y\|\mathbf{X}=\mathbf{x}) = \beta_0 + \beta_1 d$
Combination	1	$\beta_0 + \beta_1$
Patch Only	0	β_0

```
> quit = within(quit,{
+ contrasts(grp) = contr.treatment(2,base=2)
+ colnames(contrasts(grp)) = c('Combo') # Names of dummy vars -- just one
+ })
> Model1 = survreg(DayOfRelapse~grp,dist='weibull', data=quit)
> summary(Model1)

Call:
survreg(formula = DayOfRelapse ~ grp, dist = "weibull")
            Value Std. Error     z        p
(Intercept) 4.098     0.2548 16.09 3.22e-58
grpCombo    1.162     0.3999  2.91 3.67e-03
Log(scale)  0.606     0.0904  6.70 2.14e-11

Scale= 1.83

Weibull distribution
Loglik(model)= -472.1   Loglik(intercept only)= -476.5
     Chisq= 8.78 on 1 degrees of freedom, p= 0.003
Number of Newton-Raphson Iterations: 5
n= 125

> betahat = Model1$coefficients; betahat
(Intercept)    grpCombo
   4.097999    1.161901
> betahat0 = betahat[1]; betahat1 = betahat[2]
> sigmahat = Model1$scale; sigmahat
[1] 1.832392
> Vhat = vcov(Model1); Vhat
             (Intercept)     grpCombo   Log(scale)
(Intercept)  0.064903153 -0.065806535 -0.001649823
grpCombo    -0.065806535  0.159909904  0.006128624
Log(scale)  -0.001649823  0.006128624  0.008179519

> # Asymptotic covariance matrix comes out in terms of Log(scale), which is
> # a minor pain.
>
> # 1) When patients receive the combination drug therapy rather than nicotine
patch only, expected relapse time is multiplied by _______ .
>     # a) Give an estimate
>     # b) Modify the CI for beta1 to get a 95% confidence interval (don't use the
delta method).
>
> # a) Give an estimate
> exp(betahat1)
grpCombo
3.196004
```

```
> # a) Give an estimate
> exp(betahat1)
grpCombo
3.196004
>
> # b) Modify the CI for beta1 to get a 95% confidence interval (don't use the
delta method).
> L = 1.162 - 1.96*0.3999; U = 1.162 + 1.96*0.3999
> c(exp(L),exp(U))
[1] 1.459649 6.999257

> summary(Model1) # Repeating

Call:
survreg(formula = DayOfRelapse ~ grp, dist = "weibull")
            Value Std. Error     z        p
(Intercept) 4.098     0.2548 16.09 3.22e-58
grpCombo    1.162     0.3999  2.91 3.67e-03
Log(scale)  0.606     0.0904  6.70 2.14e-11

Scale= 1.83

Weibull distribution
Loglik(model)= -472.1   Loglik(intercept only)= -476.5
     Chisq= 8.78 on 1 degrees of freedom, p= 0.003
Number of Newton-Raphson Iterations: 5
n= 125
```

```
> # 2) Estimate and plot the density of relapse time for the two experimental
conditions.
>
> # Okay, lambda = exp(-mu), alpha = 1/sigma
> alpha = 1/sigmahat
> lambda0 = exp(-betahat0); lambda1 = exp(-betahat0-betahat1)
> t = seq(from=0,to=300,length=101)
> f0 = alpha*lambda0^alpha * t^(alpha-1) * exp(-(lambda0*t)^alpha)
> f1 = alpha*lambda1^alpha * t^(alpha-1) * exp(-(lambda1*t)^alpha)
> plot(t,f0,pch=' ',xlab='Day of Relapse',ylab='Density') # Empty plot
> title('Estimated Density of Relapse Time')
> lines(t,f0,lty=2); lines(t,f1,lty=1)
> # Annotate the plot
> x0=c(200,250); y0 = c(0.015,0.015); lines(x0,y0,lty=2)
> text(300,0.015,'Patch Only')
> x1=c(200,250); y1 = c(0.017,0.0171); lines(x1,y1,lty=1)
> text(300,0.017,'Combination')
```




```
> max(quit$ttr) # Maximum time value (censored)
[1] 182
```

```
> # 3) Estimate median time to relapse for the 2 groups, with Cis
```

$$E(t_i^*) \;=\; \frac{\Gamma(1+\frac{1}{\alpha})}{\lambda} = e^{\mathbf{x}_i^\top \boldsymbol{\beta}}\,\Gamma(1+\sigma)$$

$$\text{Median}(t_i^*) \;=\; \frac{[\log(2)]^{1/\alpha}}{\lambda} = e^{\mathbf{x}_i^\top \boldsymbol{\beta}}\,\log(2)^{\sigma}$$

```
> # Asymptotic covariance matrix comes out in terms of Log(scale), which is
> # unfortunate.
> # Denote log(sigma) by s, and re-write g(theta) = exp(beta0) * log(2)^sigma
> # as g(theta) = exp(beta0) * log(2)^exp(s)
> shat = log(sigmahat)
>
> # Patch Only
> medianhat0 = exp(betahat0)*log(2)^sigmahat
> # gdot will be a 1 x 3 matrix.
> gdot0 = cbind( exp(betahat0)*log(2)^exp(shat), 0, exp(betahat0) *
log(2)^exp(shat) * log(log(2)) * exp(shat) )
> se0 = sqrt( as.numeric(gdot0 %*% Vhat %*% t(gdot0)) ); se0
[1] 8.18674
> lower0 = medianhat0 - 1.96*se0; upper0 = medianhat0 + 1.96*se0
> patchonly = c(medianhat0,lower0,upper0)
> names(patchonly) = c('Median','Lower95','Upper95')
> patchonly
  Median  Lower95  Upper95
30.76581 14.71980 46.81182
>
> # Combination drug treatment
> medianhat1 = exp(betahat0+betahat1)*log(2)^sigmahat
> gdot1 = cbind( exp(betahat0+betahat1)*log(2)^exp(shat),
exp(betahat0+betahat1)*log(2)^exp(shat),
+                  exp(betahat0+betahat1) * log(2)^exp(shat) * log(log(2)) *
exp(shat) )
> se1 = sqrt( as.numeric(gdot1 %*% Vhat %*% t(gdot1)) ); se1
[1] 29.64109
> lower1 = medianhat1 - 1.96*se1; upper1 = medianhat1 + 1.96*se1
> combination = c(medianhat1,lower1,upper1)
> names(combination) = c('Median','Lower95','Upper95')
> combination
```

```
   Median   Lower95   Upper95
 98.32767  40.23114 156.42420
>
> # There is an easier way to get these numbers
> # help(predict.survreg)
> Justpatch = data.frame(grp='patchOnly')
> # A data frame with just one case and one variable.
> Combination = data.frame(grp='combination')
> treatments = rbind(Justpatch,Combination); treatments
          grp
1   patchOnly
2 combination

> # The 0.5 quantile is the median
> medians = predict(Model1,newdata=treatments,type='quantile',p=0.5,se=TRUE)
> medians
$fit
       1        2
30.76581 98.32767

$se.fit
       1        2
 8.18674 29.64109

> cbind(medians$fit,medians$se)
      [,1]     [,2]
1 30.76581  8.18674
2 98.32767 29.64109
> rbind(c(medianhat0,se0),
+       c(medianhat1,se1) )
     (Intercept)
[1,]    30.76581  8.18674
[2,]    98.32767 29.64109
>
```

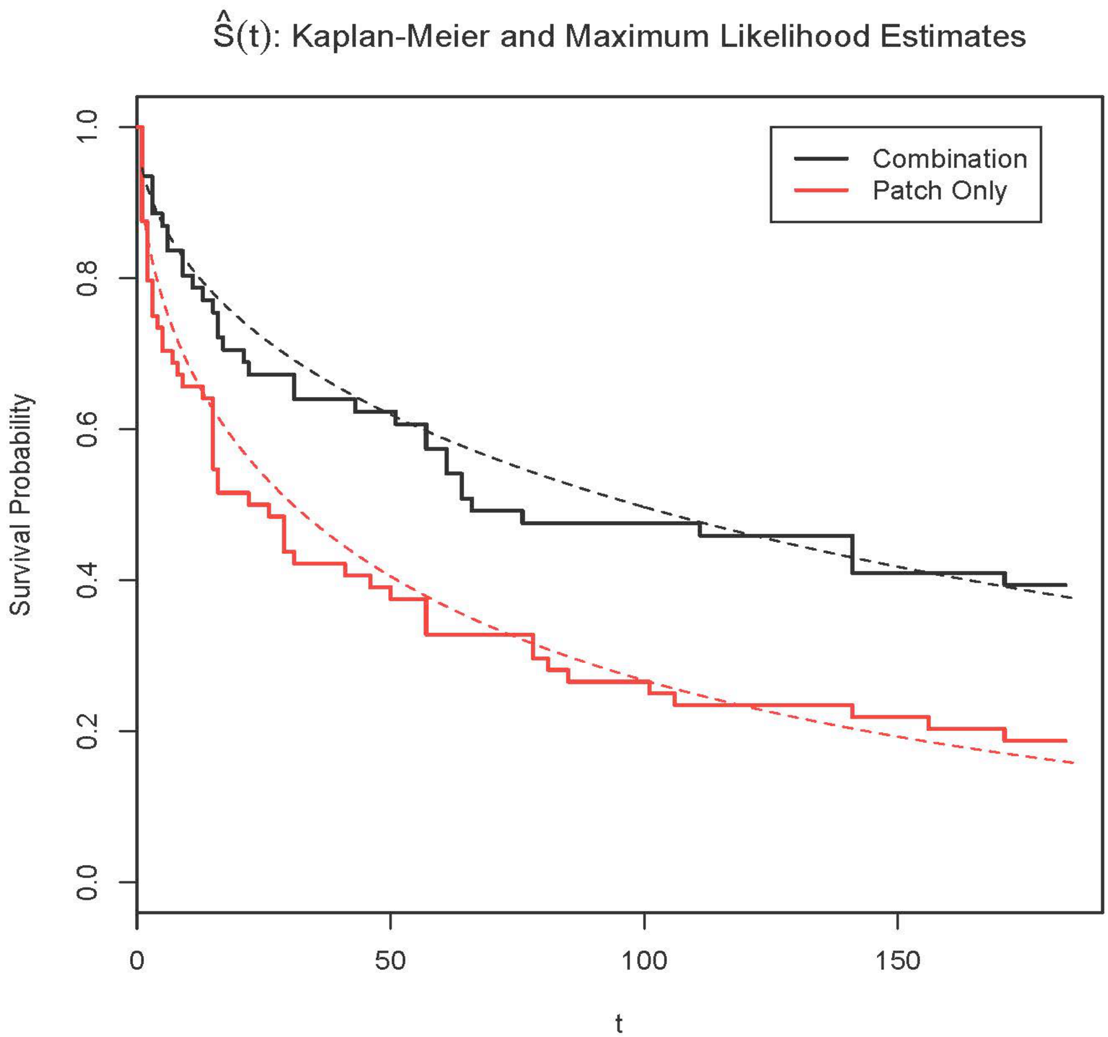
```
> # 4) Plot the Kaplan-Meier estimates and MLEs of S(t)
>
> KM = survfit(DayOfRelapse~grp, type="kaplan-meier", data=quit)
# Kaplan-Meier is the default estimation method anyway.
> summary(KM)
Call: survfit(formula = DayOfRelapse ~ grp, type = "kaplan-meier")

                grp=combination
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    1     61       4    0.934  0.0317        0.874        0.999
    3     57       3    0.885  0.0408        0.809        0.969
    5     54       1    0.869  0.0432        0.788        0.958
    6     53       2    0.836  0.0474        0.748        0.934
    9     51       2    0.803  0.0509        0.709        0.909
   11     49       1    0.787  0.0524        0.691        0.897
   13     48       1    0.770  0.0538        0.672        0.884
   15     47       1    0.754  0.0551        0.653        0.870
   16     46       2    0.721  0.0574        0.617        0.843
   17     44       1    0.705  0.0584        0.599        0.829
   21     43       1    0.689  0.0593        0.582        0.815
   22     42       1    0.672  0.0601        0.564        0.801
   31     41       2    0.639  0.0615        0.530        0.772
   43     39       1    0.623  0.0621        0.512        0.757
   51     38       1    0.607  0.0625        0.496        0.742
   57     37       2    0.574  0.0633        0.462        0.712
   61     35       2    0.541  0.0638        0.429        0.682
   64     33       2    0.508  0.0640        0.397        0.650
   66     31       1    0.492  0.0640        0.381        0.635
   76     30       1    0.475  0.0639        0.365        0.619
  111     29       1    0.459  0.0638        0.350        0.603
  141     28       3    0.410  0.0630        0.303        0.554
  171     25       1    0.393  0.0625        0.288        0.537

                grp=patchOnly
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    1     64       8    0.875  0.0413        0.798        0.960
    2     56       5    0.797  0.0503        0.704        0.902
    3     51       3    0.750  0.0541        0.651        0.864
    4     48       1    0.734  0.0552        0.634        0.851
    5     47       2    0.703  0.0571        0.600        0.824
    7     45       1    0.688  0.0579        0.583        0.811
    8     44       1    0.672  0.0587        0.566        0.797
    9     43       1    0.656  0.0594        0.550        0.784
   13     42       1    0.641  0.0600        0.533        0.770
   15     41       6    0.547  0.0622        0.438        0.684
   16     35       2    0.516  0.0625        0.407        0.654
   22     33       1    0.500  0.0625        0.391        0.639
   26     32       1    0.484  0.0625        0.376        0.624
```

```
   29     31       3    0.437  0.0620        0.331        0.578
   31     28       1    0.422  0.0617        0.317        0.562
   41     27       1    0.406  0.0614        0.302        0.546
   46     26       1    0.391  0.0610        0.288        0.530
   50     25       1    0.375  0.0605        0.273        0.515
   57     24       3    0.328  0.0587        0.231        0.466
   78     21       2    0.297  0.0571        0.204        0.433
   81     19       1    0.281  0.0562        0.190        0.416
   85     18       1    0.266  0.0552        0.177        0.399
  101     17       1    0.250  0.0541        0.164        0.382
  106     16       1    0.234  0.0530        0.151        0.365
  141     15       1    0.219  0.0517        0.138        0.348
  156     14       1    0.203  0.0503        0.125        0.330
  171     13       1    0.187  0.0488        0.113        0.312

> # Look at K-M estimates of medians
> KM[1] # Combination
Call: survfit(formula = DayOfRelapse ~ grp, type = "kaplan-meier")

      n  events  median 0.95LCL 0.95UCL
     61      37      66      51      NA
> KM[2] # Patch Only
Call: survfit(formula = DayOfRelapse ~ grp, type = "kaplan-meier")

      n  events  median 0.95LCL 0.95UCL
     64      52      24      15      57

> # Repeat MLEs for comparison
> combination
   Median   Lower95   Upper95
 98.32767  40.23114 156.42420
> patchonly
  Median  Lower95  Upper95
30.76581 14.71980 46.81182
```

```
> plot(KM,  xlab='t', ylab='Survival Probability', lwd=2, col=1:2)
> # 1 is black,  2 is red
> legend(x=125,y=1.0, col=1:2, lwd=2, legend=c('Combination','Patch Only'))
> title(expression(paste(hat(S)(t),': Kaplan-Meier and Maximum Likelihood
Estimates')))
> # MLEs
```

$$S(t) = e^{-(\lambda t)^{\alpha}} \quad \lambda = e^{-\mathbf{x}_i^{\top}\boldsymbol{\beta}} \quad \alpha = 1/\sigma$$

```
> x = 1:185
> lambda0 = exp(-betahat0); lambda1 = exp(-betahat0-betahat1); alpha=1/sigmahat
> Shat0 = exp(-(lambda0*x)^alpha); Shat1 = exp(-(lambda1*x)^alpha)
> lines(x,Shat0,lty=2,col=2) # Patch only is red
> lines(x,Shat1,lty=2)       # Combination is black (default)
```



```
>
> # Non-parametric rank test of equal survival functions
> # See http://dwoll.de/rexrepos/posts/survivalKM.html
> survdiff(DayOfRelapse~grpgrp, data=quit)
Call:
survdiff(formula = DayOfRelapse ~ grp)

                 N Observed Expected (O-E)^2/E (O-E)^2/V
grp=combination 61       37     49.9      3.36      8.03
grp=patchOnly   64       52     39.1      4.29      8.03

 Chisq= 8  on 1 degrees of freedom, p= 0.00461

> # Compare p = 0.00367 from Z-test of H0: beta1=0
>
             relapse
grp            0  1
  combination 24 37
  patchOnly   12 52
> prop.table(twoby2,1) # Proportions of row totals
             relapse
grp                   0         1
  combination 0.3934426 0.6065574
  patchOnly   0.1875000 0.8125000
> chisq.test(twoby2)

	Pearson's Chi-squared test with Yates' continuity correction

data:  twoby2
X-squared = 5.4945, df = 1, p-value = 0.01908

> fisher.test(twoby2) # p = 0.01713
```