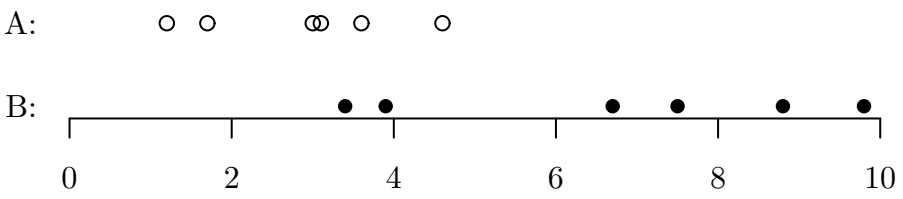
Statistics 641, Fall 2012
Homework #6
Due Dec 13, 2012

1. Suppose that we observe the following continuous responses for groups A and B.

   A: 3.0, 1.7, 4.6, 3.6, 1.2, 3.1
   B: 3.9, 6.7, 7.5, 3.4, 8.8, 9.8

   Let $\hat{\mu}$ be then difference in means, $\hat{\mu} = \bar{X}_B - \bar{X}_A$. Compute a one-sided p-value under the randomization distribution generated by the random allocation rule ($N_A = N_B$). (Note that you don't need to generate the entire randomization distribution for $\hat{\mu}$.) Compare to p-values from a two-sample t-test and Wilcoxon rank-sum test (since these are two-sided by default, you'll need to divide by 2).

First, we have $\hat{\mu} = 6.683 - 2.867 = 3.817$. A simple plot of the data shows that most of the observations in group B are well to the right of the observations in group A:



There are only small number of treatment allocations that produce a more extreme mean difference than the one observed, specifically, we need only consider allocations such that the mean in group B is at least as large as the observed mean, 6.683. These are enumerated below:

Allocated to B	mean
3.9, 4.6, 6.7, 7.5, 8.8, 9.8	6.883
3.6, 4.6, 6.7, 7.5, 8.8, 9.8	6.833
3.4, 4.6, 6.7, 7.5, 8.8, 9.8	6.800
3.1, 4.6, 6.7, 7.5, 8.8, 9.8	6.750
3.0, 4.6, 6.7, 7.5, 8.8, 9.8	6.733
3.6, 3.9, 6.7, 7.5, 8.8, 9.8	6.717
3.4, 3.9, 6.7, 7.5, 8.8, 9.8	6.683

Therefore, there are 7 allocations yielding a mean difference at least as extreme as the one observed. There are a total of

$$\binom{12}{6} = 924$$

possible allocations, so the one-sided p-value is $7/924 = .0076$.

2. Suppose that we have two treatments with a 1:1 permuted block randomization with blocks of size 6 (i.e., within each block of 6 we randomly allocate 3 to each treatment). We enroll 12 subjects and in the two blocks we observe the following summary tables:

Group	D	A	Total
1	3	0	3
2	0	3	3
	3	3	6

Group	D	A	Total
1	2	1	3
2	0	3	3
	2	4	3

(a) Calculate the size of the reference set (all possible allocations of treatments to subjects).

We have two blocks of size 6. Within each block we allocate 3 to group 1 and the remaining 3 to group 2. There are $\binom{6}{3} = 20$ ways of doing this within each block. Thus the reference set has $20 \times 20 = 400$ allocations.

(b) If x_j is the number of deaths in group 1 for block j, find the sample space for $U(0) = \sum_j x_j - E[x_j]$ and corresponding sampling probabilities under the randomization distribution. (*Hint: x_j has a hypergeometric distribution*).

In x_j be the entry in the upper left corner of block j, $j = 1, 2$.

x_1 takes 4 possible values: 0,1,2,3. $\quad E[x_1] = 3 \times 3/6 = 1.5$
x_2 takes 3 possible values: 0,1,2. $\quad E[x_1] = 2 \times 3/6 = 1$

$U(0)$ takes values according to the following table:

$x_2 \backslash x_1$:	0	1	2	3
0	-2.5	-1.5	-0.5	0.5
1	-1.5	-0.5	0.5	1.5
2	-0.5	0.5	1.5	2.5

Each x_j has a hypergeometric distribution, so if m_j is the total number of deaths in block j (3 or 2), then the x_j has probability

$$\Pr\{x_j = x\} = \frac{\binom{3}{x}\binom{3}{m_j - x}}{\binom{6}{m_j}}$$

$$\Pr\{x_1 = 0\} = \Pr\{x_1 = 3\} = \frac{\binom{3}{0}\binom{3}{3}}{\binom{6}{3}} = \tfrac{1}{20},$$

$$\Pr\{x_1 = 1\} = \Pr\{x_1 = 2\} = \frac{\binom{3}{1}\binom{3}{2}}{\binom{6}{3}} = \tfrac{9}{20}$$

Similarly,

$$\Pr\{x_2 = 0\} = \Pr\{x_2 = 2\} = \frac{\binom{3}{0}\binom{3}{2}}{\binom{6}{2}} = \tfrac{1}{5}, \qquad \Pr\{x_1 = 1\} = \frac{\binom{3}{1}\binom{3}{1}}{\binom{6}{2}} = \tfrac{3}{5}$$

Thus,

$$\begin{aligned}
\Pr\{U(0) = -2.5\} &= \Pr\{x_1 = x_2 = 0\} = \frac{1}{20} \times \frac{1}{5} = \frac{1}{100} \\
\Pr\{U(0) = -1.5\} &= \Pr\{x_1 = 1, x_2 = 0\} + \Pr\{x_1 = 0, x_2 = 1\} = \frac{9}{20} \times \frac{1}{5} + \frac{1}{20} \times \frac{3}{5} = \frac{12}{100} \\
\Pr\{U(0) = -0.5\} &= \Pr\{x_1 = 2, x_2 = 0\} + \Pr\{x_1 = 1, x_2 = 1\} + \Pr\{x_1 = 2, x_2 = 0\} \\
&= \frac{9}{20} \times \frac{1}{5} + \frac{9}{20} \times \frac{3}{5} + \frac{1}{20} \times \frac{1}{5} = \frac{37}{100}
\end{aligned}$$

By symmetry,

$$\Pr\{U(0) = 2.5\} = \frac{1}{100} \qquad \Pr\{U(0) = 1.5\} = \frac{12}{100} \qquad \Pr\{U(0) = 0.5\} = \frac{37}{100}$$

Hence $U(0)$ takes values $\{-2.5, -1.5, -0.5, 0.5, 1.5, 2.5\}$ with probabilities $\{1/100, 12/100, 37/100, 37/100, 12/100, 1/100\}$.

(c) Calculate the one-sided randomization p-value for the observed data.

The observed value of $U(0)$ is $(3 - 1.5) + (2 - 1) = 2.5$. The one-sided randomization p-value is $\Pr\{U(0) \geq 2.5\} = 0.01$ from the distribution in part (b).
(Note that the stratified chi-square statistic (Mantel-Haenszel) is $2.5^2/.708 = 8.824$ *which corresponds to a large-sample p-value of 0.003.)*

3. Suppose that we have conducted a trial with two interim analyses and a final analysis. Data from each analysis have been compiled into the data file `data6.csv` which contains the following variables:

   - `z`: Treatment variable (0,1)
   - `time1`: Follow-up time at analysis 1
   - `dead1`: Death indicator at analysis 1 (0=alive, 1=dead)
   - `time2`: Follow-up time at analysis 2
   - `dead2`: Death indicator at analysis 2 (0=alive, 1=dead)
   - `time3`: Follow-up time at analysis 3
   - `dead3`: Death indicator at analysis 3 (0=alive, 1=dead)

   For subjects who were still to be enrolled at the time of each interim analysis, the follow-up time is zero. The primary analysis is the comparison of treatment groups using the log-rank test.

(a) For each interim analysis, compute the log-rank Z-statistic. Use the convention that Z is positive if the difference favors group $z = 1$.

```
> data <- read.csv("data-final.csv")
> survdiff(Surv(time1, dead1)~z, data=data)
Call:
survdiff(formula = Surv(time1, dead1) ~ z, data = data)

       N Observed Expected (O-E)^2/E (O-E)^2/V
z=0 1122      118      125     0.446     0.936
z=1 1122      122      115     0.488     0.936

 Chisq= 0.9  on 1 degrees of freedom, p= 0.333
> survdiff(Surv(time2, dead2)~z, data=data)
Call:
survdiff(formula = Surv(time2, dead2) ~ z, data = data)

       N Observed Expected (O-E)^2/E (O-E)^2/V
z=0 1122      429      457      1.68      3.48
z=1 1122      456      428      1.79      3.48

 Chisq= 3.5  on 1 degrees of freedom, p= 0.0622
> survdiff(Surv(time3, dead3)~z, data=data)
Call:
survdiff(formula = Surv(time3, dead3) ~ z, data = data)

       N Observed Expected (O-E)^2/E (O-E)^2/V
z=0 1122      602      644      2.71      5.62
z=1 1122      646      604      2.89      5.62

 Chisq= 5.6  on 1 degrees of freedom, p= 0.0178
```

For each analysis, the Z score is the square root of the chi-square statistic, with the appropriate sign. Since the problem statement indicates that a positive Z corresponds to benefit for treatment 1, we use the observed and expected values from the above to determine the sign. In each case, the observed number of deaths in group 1 is larger than the expected, indicating that the observed treatment difference favors group 0. Hence the Z statistics are

Analysis time	Z
1	$-\sqrt{0.936} = -0.967$
2	$-\sqrt{3.48} = -1.87$
3	$-\sqrt{5.62} = -2.37$

(b) Calculate the information fraction at each interim analysis.

The information is proportional to the total number of deaths at each analysis time.

Analysis time	Deaths	Information Fraction
1	$118 + 122 = 240$	$240/1248 = 0.192$
2	$429 + 456 = 885$	$885/1248 = 0.709$
3	$602 + 646 = 1248$	1

(c) Compute the critical values for stopping boundaries at each of the two interim analysis plus the critical value at the final analysis using the power α-spending function with $\rho = 3/2$.

Assuming 2-sided $\alpha = .05$, we have:

```
> summary(bounds(c(.192, .709, 1), iuse=c(3,3), phi=c(3,3)/2,
+    alpha=c(.025,.025)))

Lan-DeMets bounds for a given spending function

n =  3
Overall alpha:  0.05

Type: Two-Sided Symmetric Bounds
Lower alpha:  0.025
Upper alpha:  0.025
Spending function:  Power Family: alpha * t^phi

Boundaries:
    Time    Lower   Upper   Exit pr.  Diff. pr.
1  0.192  -2.8622  2.8622  0.0042065  0.0042065
2  0.709  -2.2157  2.2157  0.0298497  0.0256431
3  1.000  -2.1166  2.1166  0.0500000  0.0201503
```

(d) What can you conclude?

The Z statistics at each of the interim analyses are within the monitoring boundaries, so the trial would not have stopped early on that basis. At the final analysis, the Z crosses the lower boundary, so we would have demonstrated that treatment 0 is superior to treatment 1.

(e) Calculate the conditional power at each interim analysis given the alternative hypothesis H_A: $\beta = .223$ where β is the log-hazard ratio (corresponding to a hazard ratio of 1.25 favoring group $z = 1$).

Conditional power is given by

$$1 - \Phi\left(\frac{b_K - B(t) - (1-t)\theta}{\sqrt{1-t}}\right)$$

where $K = 3$, $b_K = 2.1166$ (from the table in part (b)), $B(t) = \sqrt{t}Z(t)$ with $t = 0.192$ or 0.709 at analyses 1 and 2 respectively, and $Z(t)$ is the observed Z at analysis time t. We compute as $\theta = \beta\sqrt{\mathcal{I}_K}$, where $\mathcal{I}_K = 1248/4 = 312$, one-fourth of the total number of events. $\theta = .223\sqrt{312} = 3.939$.

Plugging into the formula we have at analysis 1:

$$1 - \Phi\left(\frac{2.1166 - \sqrt{.192} \times (-.967) - (1 - 0.192) \times 3.939}{\sqrt{1 - 0.192}}\right) = 1 - \Phi(-0.710) = 0.761$$

At analysis 2:

$$1 - \Phi\left(\frac{2.1166 - \sqrt{.709} \times (-1.87) - (1 - 0.709) \times 3.939}{\sqrt{1 - 0.709}}\right) = 1 - \Phi(4.72) = 0.000001$$

Based on conditional power, there is still a substantial likelihood of success (showing benefit for treatment 1) at the first analysis where conditional power is 76%. However, at analysis 2, the probability of success assuming that the true $\beta = .233$, is miniscule. The trial could be stopped on that basis.

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