Exam 1

Steven Chiou

Instructions

- Due date: **Tuesday, November 13**.
- This is a open resource exam, but you are not allowed to ask post exam questions online.
- You are not allowed to collaborate with classmates and/or people outside of class.
- Please circle or highlight your final answer.
- The toal possible point is 80.

Violation of this agreement will result in an **F** on this exam and it will be averaged in as a 0%.

---

1. **Use the complete *WHAS100* dataset and gender as the group indicator, compute the log-rank statistic, Q, presented as Equation (9) on page 60 of note 2 with $\omega_i = 1$. Use Q to compute a p-value to test the null hypothesis of $H_o : S_0(t) = S_1(t)$. Do this *without a software package* (6 pts), and verify the calculation with `survdiff` (4 pts).**

Solution:
We will first load the `tidyverse` package (but not the `survival` package):

```
> library(tidyverse)
```

The following codes calculates the necessary quantities to calculate Q:

```
> attach(whas100)
> dat <- tibble(Time = unique(sort(lenfol[fstat > 0]))) %>%
+     mutate(ni = colSums(outer(lenfol, Time, ">=")),
+            di = colSums(outer(lenfol, Time, "==")),
+            ni.1 = colSums(outer(lenfol[gender == 1], Time, ">=")),
+            di.1 = colSums(outer(lenfol[gender == 1], Time, "==")),
+            ni.0 = ni - ni.1, di.0 = di - di.1,
+            E = ni.1 * di / ni, V = ni.1 * ni.0 * di * (ni - di) / ni / ni / (ni - 1))
> detach(whas100)
```

Compute Q:

```
> with(dat, sum(di.1 - E)^2 / sum(V))
```

```
[1] 3.971377
```

2. **There are many ways to form a basis for survival curve comparison. Here are some:**
   a. **The numerator term in Q without the square:**

$$D_1 = \sum_{i=1}^{D} \{d_{1i} - E(d_{1i})\}.$$

   b. **The largest distance between the two curves:**

$$D_2 = \max |S_1(t) - S_0(t)|.$$

   c. **The difference between the median survival times:**

$$D_3 = S_1^{-1}(0.5) - S_0^{-1}(0.5)$$

   d. **The difference between the mean survival times:**

$$D_4 = \int_0^{t_{(n)}} \{S_1(u) - S_0(u)\}\, du,$$

   where $t_{(n)}$ is the maximum observed survival time.
   Compute each of the above statistic for the $WHAS100$ dataset (5 pts $\times 4$).

Solution:
Taking advantage of the `dat` created in #1, these quantity can be easily computed with the following codes:
a.

```
>   with(dat, sum(di.1 - E))
```

```
[1] 6.62
```

b.

```
>   dat <- dat %>% mutate(km0 = cumprod((ni.0 - di.0) / ni.0),
+                         km1 = cumprod((ni.1 - di.1) / ni.1))
>   max(abs(dat$km0 - dat$km1))
```

```
[1] 0.3853606
```

c.

```
> with(dat, Time[which.max(km1 <= .5)] - Time[which.max(km0 <= .5)])
```

```
[1] -818
```

d.

```
> with(dat, sum(-diff(rev(Time)) * rev(km1 - km0)[-1]))
```

```
[1] -428.7407
```

3. **The statistics computed in (2) do not provide meaningful interpretations when standing along. We will use a permutation approach to test for the null hypothesis of $H_o : S_0(t) = S_1(t)$ based on these statistics. The idea of a permutation test is simple. The general procedure can be summarized into the following steps:**
   i. **Compute the desired statistic based on the observed data; we will call this the observed statistic.**
   ii. **Permute the data under the null.**
   iii. **Compute the statistics for each possible permutation in Step ii.; we will call these permutation statistics.**
   iv. **Draw conclusion based on where the observed statistic stands among the permutation statistics.**

   The statistics we computed in (2) are the observed statistics in Step i. If the null hypothesis of $H_o : S_0(t) = S_1(t)$ is true, then one can randomly shuffle the group indicator to generate different permutations (Step ii) and the statistics for these permutations should be similar (Step iii).

   a. **(5 pts×4) Generate 5000 permutation and, for each of the permutation, compute the four statistics presented in (2). We will call the permutated statistics D^*_{1i}, D^*_{2i}, D^*_{3i} and D^*_{4i} for $i = 1, \ldots, 5000$. Create a histgram for these permutated statistics and print the `summary`.**
   b. **(5 pts×4) Compute the p-value based on these statistics by**

$$p = 2 \cdot \frac{\min(N_1, N_2)}{5000},$$

   where $N_1 = \#\{D \geq D^*\}$, $N_2 = \#\{D \leq D^*\}$, and # means the "number of", e.g., N_1 is the number of these permutated statistics less than or equal to the observed statistic.

Solution:
We first prepare a function that returns the 4 statistics in #2:

```
> #' @param obs is the observed survival time
> #' @param event is the censoring indicator
> #' @param x is the categorical covariate; taking values of 0 and 1
> getD <- function(obs, event, x) {
+     dat0 <- tibble(Time = unique(sort(obs[event > 0]))) %>%
+         mutate(ni = colSums(outer(obs, Time, ">=")),
+                di = colSums(outer(obs, Time, "==")),
+                ni.1 = colSums(outer(obs[x > 0], Time, ">=")),
+                di.1 = colSums(outer(obs[x > 0], Time, "==")),
+                ni.0 = ni - ni.1, di.0 = di - di.1,
+                E = ni.1 * di / ni, V = ni.1 * ni.0 * di * (ni - di) / ni / ni / (ni - 1),
+                km0 = pmax(0, cumprod((ni.0 - di.0) / ni.0), na.rm = TRUE),
+                km1 = pmax(0, cumprod((ni.1 - di.1) / ni.1), na.rm = TRUE))
+     attach(dat0)
+     d1 <- sum(di.1 - E)
+     d2 <- max(abs(km0 - km1))
+     d3 <- Time[which.max(km1 <= .5)] - Time[which.max(km0 <= .5)]
+     d4 <- sum(-diff(rev(Time)) * rev(km1 - km0)[-1])
+     detach(dat0)
+     c(d1 = d1, d2 = d2, d3 = d3, d4 = d4)
+ }
```

Check the function with `whas100` to confirm it returns values in #2:

```
> (d0 <- with(whas100, getD(lenfol, fstat, gender)))
```

```
         d1          d2          d3          d4
  6.6199997   0.3853606 -818.0000000 -428.7407041
```

a. The following codes perform the permutation statistics based on 5000 permutation:

```
> set.seed(123)
> system.time(
+   permd <- t(replicate(5000, with(whas100, getD(lenfol, fstat, sample(gender)))))
+   )
```

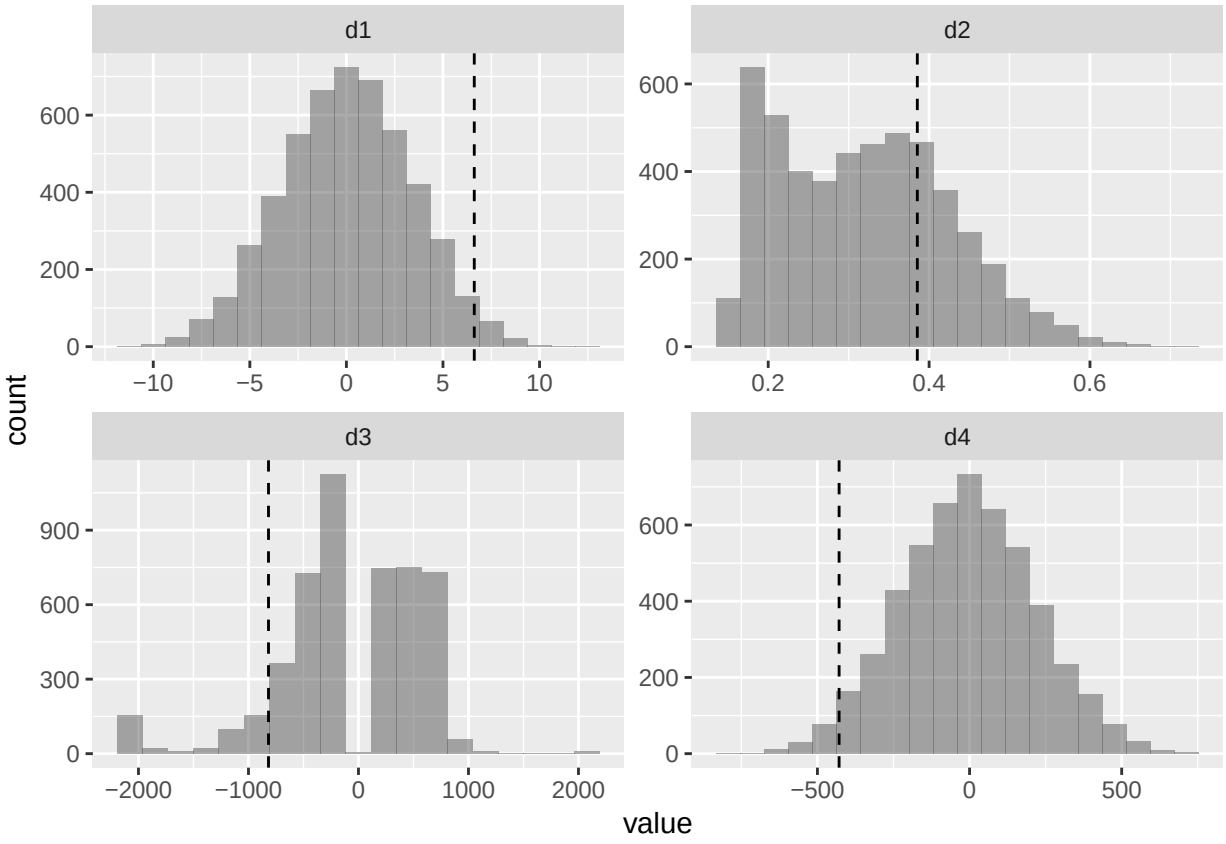
```
   user  system elapsed
 20.632   0.020  20.674
```

The following codes print the summary and produce the histogram

```
> summary(permd)
```

```
       d1                  d2                d3          
 Min.   :-11.78196   Min.   :0.1439   Min.   :-2195.00  
 1st Qu.: -2.25294   1st Qu.:0.2229   1st Qu.: -395.00  
 Median :  0.05511   Median :0.3154   Median : -136.00  
 Mean   :  0.02653   Mean   :0.3189   Mean   :  -81.82  
 3rd Qu.:  2.31044   3rd Qu.:0.3931   3rd Qu.:  390.00  
 Max.   : 11.97221   Max.   :0.7143   Max.   : 2195.00  
       d4          
 Min.   :-763.848  
 1st Qu.:-154.421  
 Median :  -4.830  
 Mean   :  -4.286  
 3rd Qu.: 146.719  
 Max.   : 743.986  
```

```
> ggdat <- gather(as.tibble(permd), "d", factor_key = TRUE) %>% mutate(d0 = unlist(d0[d]))
> ggplot(ggdat, aes(value)) +
+     geom_histogram(alpha = .5, bins = 20) + geom_vline(aes(xintercept = d0), lty = I(2)) +
+     facet_wrap(d ~., scale = "free")
```



b.

The p-values are

```
> sapply(1:4, function(x) 2 * min(sum(d0[[x]] < permd[,x]), sum(d0[[x]] > permd[,x])) / 5000)
```

```
[1] 0.0460 0.5532 0.1748 0.0532
```

4. **Another method to compare two survival curves is to consider a sign test. Suppose we have two groups of uncensored survival times:**

   Males: $x_1, x_2, \ldots, x_{n_0}$.

   Females: $y_1, y_2, \ldots, y_{n_1}$.

   The sign test looks at the statistic

$$U = \sum_{i=1}^{n_0} \sum_{j=1}^{n_1} \text{sgn}(x_i - y_j),$$

   where sgn$(\cdot)$ is the sign function. In the pretense of right censoring, survival times can not be compared directly and a modified version of $U = \sum_{i=1}^{n_0} \sum_{j=1}^{n_1} U_{ij}$ is considered, where

$$U_{ij} = \begin{cases} 1 & \text{if } x_i > y_j, y_j \text{ is uncensored.} \\ -1 & \text{if } x_i < y_j, x_i \text{ is uncensored.} \\ 0 & \text{otherwise.} \end{cases}$$

   a. **(5 pts) Compute U for the WHAS100 dataset.**
   b. **(5 pts) Create a histgram for these permutated statistics and print the `summary`. Obtain a permutation p-value based on 5000 permutations.**

Solution:
We will take a similar approach as in #3; first write a function to compute U then use it for permutation. The following function can be used to compute U:

```
> getU <- function(obs, event, x) {
+     t1 <- obs[x > 0]
+     d1 <- event[x > 0]
+     t0 <- obs[x == 0]
+     d0 <- event[x == 0]
+     sum(outer(t0, t1[d1 > 0], ">")) - sum(outer(t0[d0 > 0], t1, "<"))
+ }
```

a. For the `whas100` data:

```
> (U0 <- with(whas100, getU(lenfol, fstat, gender)))
```

```
[1] 459
```

b. Perform permutation test, calculate p-value and produce histogram:

```
> set.seed(123)
> system.time(permU <- replicate(5000, with(whas100, getU(lenfol, fstat, sample(gender)))))
```

```
   user  system elapsed
  0.255   0.015   0.271
```

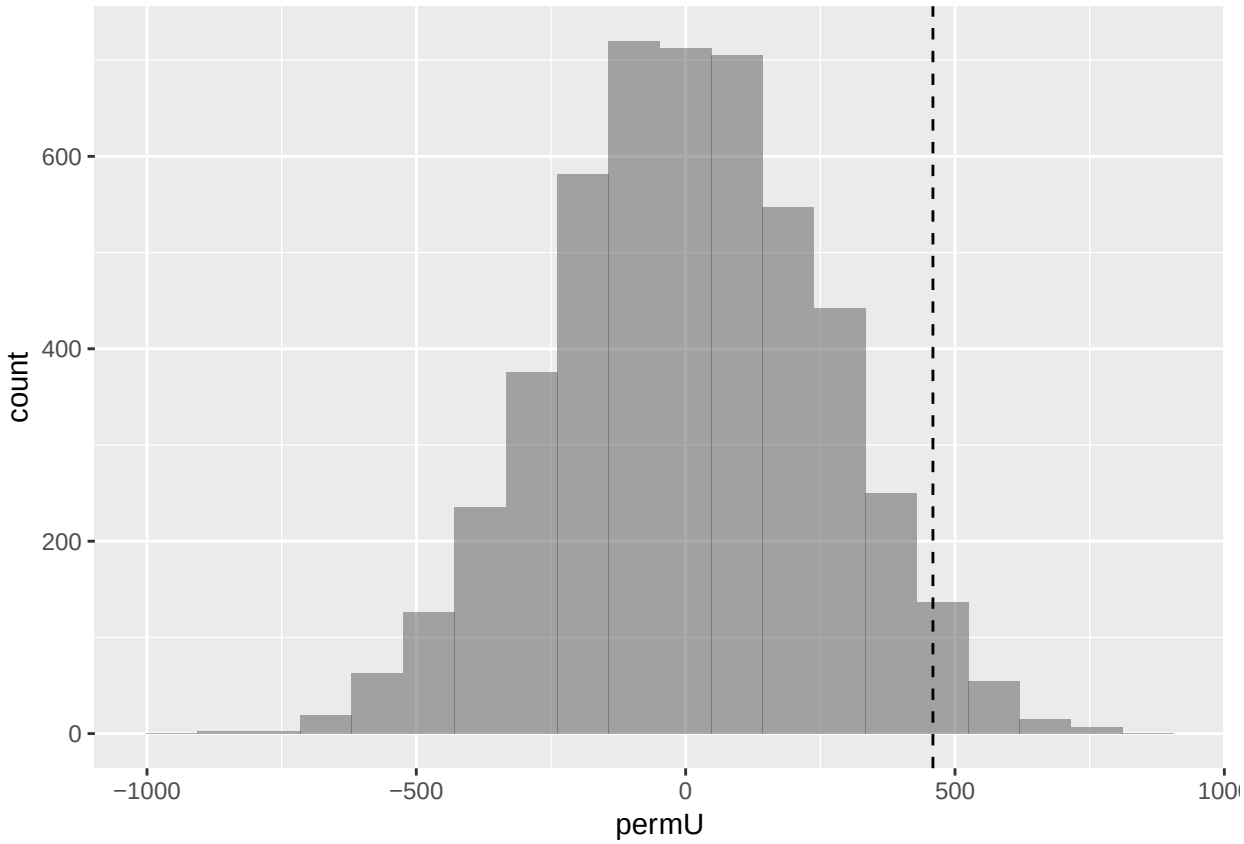
```
> summary(permU)
```

```
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
-916.000 -166.000    2.000    3.146  177.000  896.000
```

```
> 2 * min(sum(U0 < permU), sum(U0 > permU)) / 5000
```

```
[1] 0.0644
```

```
> ggplot() + aes(permU) + geom_histogram(alpha = .5, bins = 20) +
+   geom_vline(aes(xintercept = U0), lty = I(2))
```


600
400
200
0
count
−1000
−500
0
500
permU