12. Nonparametric Methods

Readings: Chihara and Hesterberg: 3.3-3.4
Rosner: 9.1-6

R: expand.table(epitools package), sample function, exactRankTests (package)

Homework: Homework 5 due by noon on October 8
Homework 6 due by noon on October 15

Overview

A) Permutation tests
B) Wilcoxon rank sum
C) Wilcoxon signed rank (paired quantitative data – see Rosner for details)
D) Sign test (paired qualitative data – see McNemar's test, Lecture 10)

Up until now we have mostly considered parametric procedures, i.e. those that, based on the central limit theorem, depend on the *normality of the statistics* being computed.

Nonparametric methods are useful when the assumption of normality does not hold (e.g. small samples, heavily skewed data, ordinal data).

A. Permutation tests

TWO-SAMPLE PERMUTATION TEST

Pool the $m + n$ values.

repeat

Draw a resample of size m without replacement.

Use the remaining n observations for the other sample.

Calculate the difference in means or another statistic that compares samples.

until we have enough samples

Calculate the P-value as the fraction of times the random statistics exceed the original statistic. Multiply by 2 for a two-sided test.

Optionally, plot a histogram of the random statistic values.

Source: Chihara and Hesterberg

Required assumption: under the null hypothesis, the distribution for the two groups is equal.

Note! The distribution doesn't have to be normal. It can be anything, so as long as the two populations (groups) have the same distribution under the null hypothesis. Thus, group labels are said to be *exchangeable*. Differences in spread under H_0 can yield misleading results.

The summary statistic for each permutation can be a difference in means, medians, proportions, etc. so the approach can be easily generalized.

Example: Contingency Tables and Hypothesis Tests

Survey data from 2001 on support for marijuana for medicinal purposes: Does support for medical marijuana depend on age? (H_0: no association between age and favoring use of medical marijuana)

Age group	Response	
	For	Against
18-29 yo	172	52
30-49 yo	313	103
$\geq$50 yo	258	119

We need to transform this summary data into individual level data:

Person	Age group	Response
1	18-29 yo	For
2	18-29 yo	For
.	.	.
.	.	.
.	.	.
1017	$\geq$50 yo	Against

$\Leftarrow$ **Individual level data**

How do we generate a null distribution for this statistic?

- Use a chi-square distribution with (r-1)x(c-1) degrees of freedom (Lecture 10, Section C)
- Permutation (Lecture 7, Section B1)

PERMUTATION TEST FOR INDEPENDENCE OF TWO VARIABLES

Store the data in a table with one row per observation and one column per variable.
Calculate a test statistic for the original data. Normally large values of the test statistic suggest dependence.
repeat
  Randomly permute the rows in one of the columns.
  Calculate the test statistic for the permuted data.
until we have enough samples
Calculate the *P*-value as the fraction of times the random statistics exceed the original statistic.
Optionally, plot a histogram of the resampled statistic values.

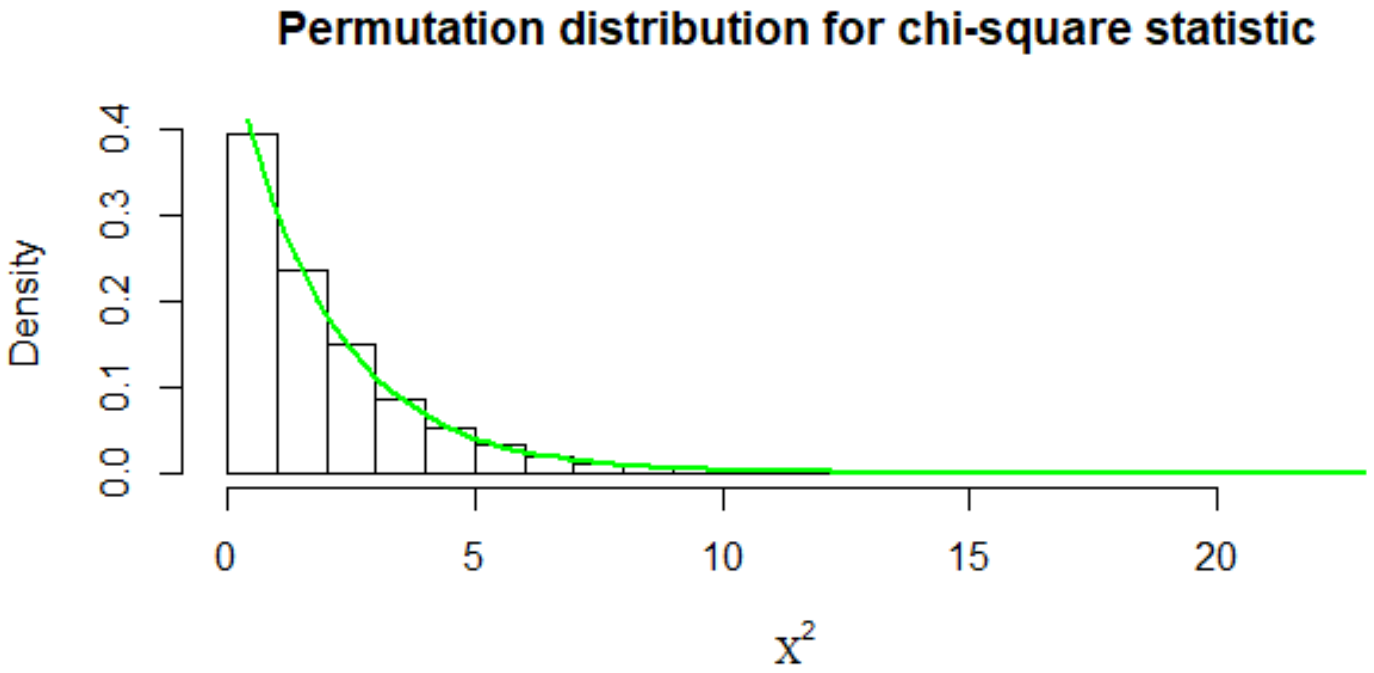
Source: Chihara and Hesterberg

R code

```
X <- matrix(nrow=3, byrow=T, c(172,52,313,103,258,119),
+               dimnames=list(c("18-29","30-49",">50"),c("for","against")))

# Obtain row proportions in the table
prop.table(X, margin=1)
             for   against
18-29 0.7678571 0.2321429
30-49 0.7524038 0.2475962
>50   0.6843501 0.3156499

library(epitools)

dat <- expand.table(X)

# define a function to do the chisquare test

chisq<-function(Obs){
+   #Obs is the observed contingency table
+   Expected <- outer(rowSums(Obs),colSums(Obs))/sum(Obs)
+   sum((Obs-Expected)^2/Expected)
}

# do a permutation test
# first compute observed statistic

agegrp <- dat[,1]
response <- dat[,2]

observed <- chisq(table(agegrp, response)) #2 degrees of freedom: (r-1)(c-1)
observed
[1] 6.681429
```

R code cont.

```
B <- 10^5-1  #set number of times to repeat this process result
result <- numeric(B) # space to save the random differences

for(i in 1:B){
+   agegrp.permuted <- sample(agegrp) #sample group labels without replacement
+   perm.table <- table(agegrp.permuted, response)
+   result[i] <- chisq(perm.table)
}

##Plot
hist(result, freq=FALSE, xlab = expression(Chi^2), main="Permutation distribut
ion for chi-square statistic")
abline(v = observed, col = "blue", lty=5)
curve(dchisq(x, 2), add=TRUE, col="green", lwd=2)
```



R code cont.

```
#Compute p-value from the permutation distribution
(sum(result >= observed)+1)/(B + 1)  #P-value
[1] 0.03661

# compute p-value from chi-square distribution
1-pchisq(observed, df=2)
[1] 0.03541165
```

Conclusion:

Practical notes on permutation testing:

- Various statistics can be used: e.g. mean, median, proportions, etc.
- For more precision, a larger number of permutations should be used.
- Sampling (entire) permutations without replacement is most appropriate but with replacement is acceptable and faster.
- Any strictly increasing function of the statistic will yield the same p-value.
- Adding 1 to the numerator and denominator corresponds to using the observed sample as part of the null distribution
- For two-sided alternative hypotheses, conduct both one-sided tests and multiply the smaller p-value by 2. (In our case the chi-squared test takes the squared part into account, so we don't need to multiply by 2 even though it is a two-sided test.)
- Normality of underlying distributions not assumed. Robust to skewness and imbalance as long as the underlying distributions are equal under the null hypothesis.
- No random sampling assumption is required. Inference to a population can't then be made but a conclusion about the sample can be drawn. However, treatment (exposure) assignments are assumed to be random.

B. Wilcoxon rank sum test (*aka* Mann Whitney U test; for two independent samples, quantitative data)

The nonparametric two independent sample test is "analogous" to the parametric independent sample *t*-test, but it has nothing to do with comparing means (or medians!).

Assumptions:

- Independent observations (random sampling)
- The two distributions have the same shape but they have different location parameters (symmetry is not a necessary assumption).
- The test is based on the P(an observation in sample 1 > an observation in sample 2) – H_0: $P(X_1 > X_2) + P(X_1 = X_2) = 0.5$ vs. H_1: $P(X_1 > X_2) + P(X_1 = X_2) \neq 0.5$.
- Does not require normality, even for small n
- For large enough samples ($n_1 \geq 10$ and $n_2 \geq 10$) use normal approximation form of the test; for small *n* use Table 12 in the Rosner text. When using the tables caution should be exercised when there are a lot of ties in the data.

Procedure:
Pool the 2 samples and rank the observations, computing average ranks for observations in a group with the same value.

If $n_1 \geq 10$ and $n_2 \geq 10$ we can use a normal approximation, otherwise we need to use the tabled critical values which are derived from **exact** distributions of the **sum of the ranks** based on **permutation theory** with ranks of the data measurements used, not the measurements themselves.

For the asymptotic test:
R_1 = sum of the ranks in one sample (choice is arbitrary---some tables require choosing the smaller of the two sums)

$$E[R_1] = \frac{n_1(n_1+n_2+1)}{2}, V[R_1] = \left(\frac{n_1 n_2}{12}\right)\left[n_1 + n_2 + 1 - \frac{\sum_{i=1}^{g}(t_i^3 - t_i)}{(n_1+n_2)(n_1+n_2-1)}\right]$$

If there are ties, we need to correct the variance for the ties occurring between samples where g = number of distinct tied values and t_i = number of ties at a specific value (the portion of $V[R_1]$ after the minus sign). Finally we calculate our Z statistic to compare:

$$Z = \frac{|R_1 - E[R_1]| - 0.5}{\sqrt{V[R_1]}}$$

If either sample size is less than 10, a small-sample table of exact significance levels must be used. These are based on enumeration of all possible permutations of the data and the resulting possible rank sums. Table 12 in the Rosner text gives upper and lower critical values for the rank sum statistic $\mathbf{T = R_1}$ for a two-sided test. In general, the results are statistically significant at a particular α-level if $T \leq T_l$ = the lower critical value or $T \geq T_r$ = the upper critical value.

Note: the Mann-Whitney U test is computed differently but is completely equivalent to the Wilcoxon rank sum test.

Example. *Ophthalmology*. Different genetic types of the disease retinitis pigmentosa (RP) are thought to have different rates of progression with the dominant form of the disease progressing the most slowly, the recessive form of the disease the next most slowly, and the sex-linked form of the disease progressing most quickly.

This hypothesis can be tested by comparing the visual acuity of people ages 10-19 who have different genetic types of RP. Suppose there are 25 people with dominant disease and 30 people with sex-linked disease. The best corrected visual acuities (i.e. with appropriate glasses) in the better eye of these people are presented below. How can these data be used to test if the **distribution** of visual acuity is different between the two groups?

Visual Acuity	Dominant	Sex-linked	Combined Sample	Range of Ranks	Average Rank
20-20	5	1	6	1-6	3.5
20-25	9	5	14	7-20	13.5
20-30	6	4	10	21-30	25.5
20-40	3	4	7	31-37	34
20-50	2	8	10	38-47	42.5
20-60	0	5	5	48-52	50
20-70	0	2	2	53-54	53.5
20-80	0	1	1	55	55
	25	30	55		

Manual Calculation:

Since $n_1 \geq 10$ and $n_2 \geq 10$, we can use the normal approximation
R_1 = sum of the ranks in one sample = 5(3.5) + 9(13.5) + 6(25.5) + 3(34) + 2(42.5) = 479

$$E[R_1] = \frac{n_1(n_1 + n_2 + 1)}{2} = \frac{25(25 + 30 = 1)}{2} = 700$$

$$V[R_1] = \left(\frac{n_1 n_2}{12}\right)\left[n_1 + n_2 + 1 - \frac{\sum_{i=1}^{g}(t_i^3 - t_i)}{(n_1+n_2)(n_1+n_2-1)}\right]$$

$$= \left(\frac{(25)30}{12}\right)\left[56 - \frac{(6^3 - 6) + (14^3 - 14) + \cdots + (2^3 - 2)}{55(54)}\right] = 3386.74$$

$$Z = \frac{|R_1 - E[R_1]| - 0.5}{\sqrt{V[R_1]}} = \frac{|479 - 700| - 0.5}{\sqrt{3386.74}} = 3.7887$$

$$p = 2 \times \big(1 - \Phi(3.79)\big) = 2 \times (1 - 0.9999247) = 0.00015$$

R code

```
Y <- matrix(nrow=8, byrow=T, c(5,1,9,5,6,4,3,4,2,8,0,5,0,2,0,1),
            dimnames=list(c(20,25,seq(30,80,10)),c("dom","sexlink")))

eye.test <- expand.table(Y)
colnames(eye.test) <- c('acuity','grp')
eye.test$acuity <- as.numeric(eye.test$acuity)
eye.test$d_sl <- as.numeric(eye.test$grp)

library(exactRankTests)

# Two-sided exact test
wilcox.exact(acuity~d_sl,eye.test)

      Exact Wilcoxon rank sum test

data:  acuity by d_sl
W = 154, p-value = 8.496e-05 # W is the Mann-Whitney U statistic - see p.15
alternative hypothesis: true mu is not equal to 0 # mu is the location shift
parameter for the two distributions, not really the best statement, we're comp
aring the distributions of the two samples/groups

# Two-sided asymptotic test
wilcox.exact(acuity~d_sl,eye.test ,exact=F)

      Asymptotic Wilcoxon rank sum test

data:  acuity by d_sl
W = 154, p-value = 0.0001461
alternative hypothesis: true mu is not equal to 0
```

(Note: R calculates W as $R_1 - n_1(n_1+1)/2$.) Conclusion:

Alternative way of computing the test

- The Mann-Whitney U test. Test statistic is a U statistic: the number of times an observation from distribution 2 is less than an observation from distribution 1. Here, "less than" means "worse acuity".

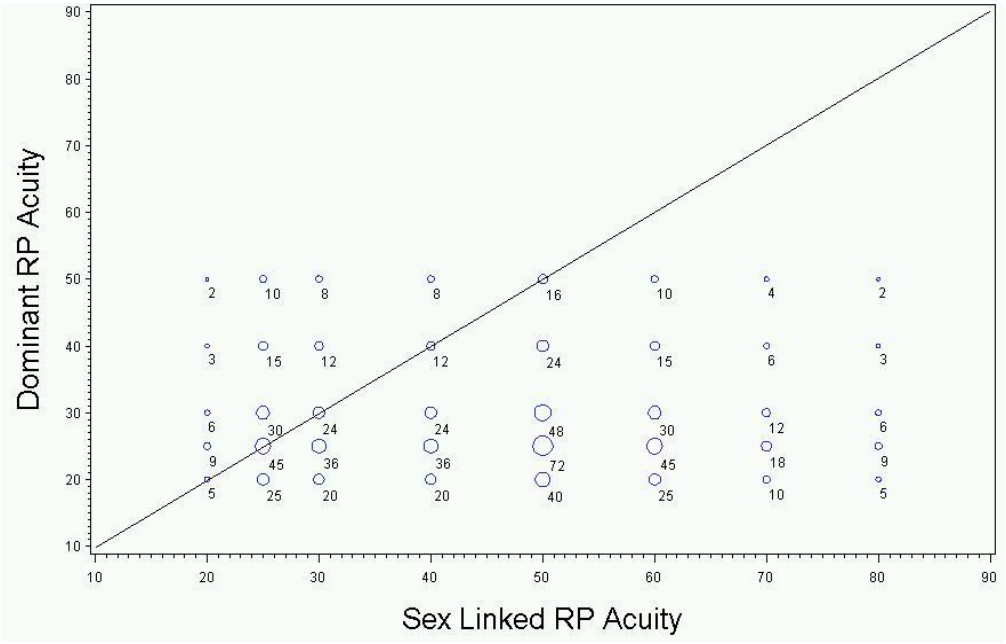
- The test is based on the P(an observation in sample 1 > an observation in sample 2) – H_0: $[P(X_1 > X_2) + P(X_1 = X_2)] = 0.5$ vs. H_1: $[P(X_1 > X_2) + P(X_1 = X_2)] \neq 0.5$.

- $\frac{U}{mn} = p'' = P(X_1 > X_2)$

- In this case *mn* = 25*30=750 – the number of pairs where one member is in the dominant and one is in the sex linked group, with acuity for dominant, X_2, and X_1 for sex linked, U = 2+10+8+8+3+15+12+6+30+9 + (5+45+24+12+16)/2 = 103 + 102/2 (these are the pairs in which the acuity is tied; they receive a weight of ½) = 103+51 = 154, and p" = P(Sex Linked RP VA > Dominant RP VA) = 154/750 = 0.187.

Visualization of the Wilcoxon-Mann-Whitney test

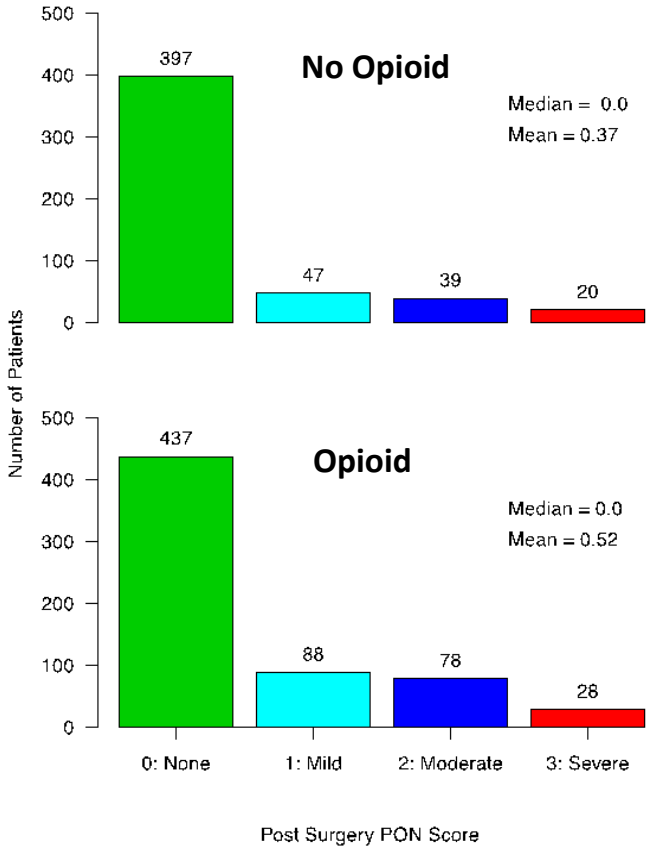
H_0: P(Dominant RP VA < Sex linked RP VA) = 0.5, i.e. the proportion of bubble *areas* below the identity line = 0.5, where each bubble represents the number of Sex Linked/Dominant pairs with that combination of VA.



Be aware that several authors (including Rosner) <u>mistakenly</u> refer to the WMW test as a **test of the medians**! ☹

Counterexample: Equal Medians, but a significant difference using WMW test - Aromatherapy Study

- Primary outcome measure: a four level verbal descriptive scale (VDS) for nausea (0: none; 1: mild; 2: moderate; 3: severe)
- Opioid medication for reduction of post-operative pain
- WMW test provides a p-value of 0.001.



Notes

- Efficiency
  - WMW is ~95% efficient against the 2-sample t-test for normally distributed samples;
  - more efficient than 2-sample t-test for many heavy tailed distributions;
  - compared to the t-test the efficiency of the rank sum test is never less than 0.864.
- When using the tables caution should be exercised when there are a lot of ties in the data.
- The Rank Sum Test has a very unintuitive feature: it can lack transitivity! This means that it's possible to see the following contradictory results, as an example – $P(X_1 > X_2) > 0.5$, $P(X_2 > X_3) > 0.5$, but $P(X_3 > X_1) > 0.5$. For more on this, see http://www.emersonstatistics.com/courses/formal/b517_2010/b514hw6key.pdf, section 8.
- A remedy for this is to use a test that compares the multiple groups all at once instead of as pairwise tests. It's called the Kruskal-Wallis test and it's analogous to one-way analysis of variance (ANOVA) which we will start talking about in a few lectures.
- Nevertheless, you will see the WMW test used widely in the literature in situations where there are small samples and/or heavily skewed/kurtotic data.
- Two relevant papers on the WMW test are posted in the Canvas Paper Repository:
  - Fagerland, 2012
  - Divine et al., 2017

C. Wilcoxon Signed Rank Test (quantitative paired data)

A related test, the Wilcoxon Signed Rank test incorporates the sign and magnitude of the differences in the paired data setting. It is also useful when the outcome variable describes ordering but not necessarily physical distance or difference (unequal magnitude/distance between points – ordinal vs. discrete scale).

e.g. a Likert scale: Patient is 1 = much improved, 2 = slightly improved, 3 = same, 4 = slightly worse, 5 = much worse

The test is based on the paired differences:
H_0: $[P(X_1 + X_2 < 0)] = 0.5$

Most texts treat this as a test of the median difference which is not correct, but the quantity in H_0 above is not as interpretable as $[P(X_1 > X_2) + P(X_1 = X_2)] = 0.5$ is for the WMW test.

For more details, see Divine, G., Norton, H., Hunt, R., & Dienemann, J. (2013). A Review of Analysis and Sample Size Calculation Considerations for Wilcoxon Tests. *Anesthesia & Analgesia*, 699-710.

***Frank Wilcoxon* (1882 -1965)**

Frank Wilcoxon was born in Glengarriffe Castle, near Cork, Ireland, to wealthy American parents. He was soon brought to the United States where he attended Pennsylvania Military College, Rutgers, and Cornell. After receiving his doctorate as a physical chemist, Wilcoxon joined the Boyce Thompson Institute for Plant Research and began to study the use of copper compounds as fungicides. While doing so, he became part of a group, along with W. J. Youden (Biography 5.1), that studied the newly published *Statistical Methods for Research Workers* by Ronald A. Fisher (Biography 13.1). Through these achievements (and either in spite or because of his lifelong preoccupation with biochemistry, plant pathology, and entomology), he became a significant member of that small group of twentieth-century pioneers who developed new statistical methodology. In a now famous 1945 paper, he presented the *rank-sum test* and the *signed-rank test* now named after him. The basic idea of replacing actual sample data by their ranks, which seems so utterly simple in retrospect, proved to be inspirational to the further development of the entire field of nonparametric statistics. The elegant simplicity of these tests led to their widespread adoption and the fact that Wilcoxon in 1945 was not even aware of all the advantages of his new methods does not dim the luster of his contribution.

These advantages, not all of them discussed in text Chapter 21, include the ease and rapidity of calculation, the availability of exact significance levels without the restrictive normality assumption, the relative insensitivity to outlying sample observations, the invariance under certain monotonic transformations of the data, the applicability to situations where the data are ordinal, the excellent power properties for wide classes of alternative distributions, and the availability of distribution-free confidence intervals for the location parameters of interest. In addition, Wilcoxon contributed mightily to other aspects of statistics, in particular biological assay methods and sequential analysis (discussed in text Chapter 23). *Source:* Adapted from *International Encyclopedia of Statistics*, vol. 2 (New York: The Free Press, 1978), pp.1245-1250.