STAT 226 Lecture 7

Section 2.6 Fisher's Exact Tests

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Textbook Coverage

- 2.6.1-2.6.2 Fisher’s Exact Test
- Ignore other subsections in Section 2.6

Hypergeometric Distributions

R red balls, B blue balls

↙ ↘

d balls drawn at random without replacement

X red, $d-X$ blue

$A+B-d$ Balls remained in the original box

$R-X$ red, $B-(d-X)$ blue

Suppose d draws are made at random w/o replacement from a box containing R red balls and B blue balls. The number of red balls X obtained in d draws has a **hypergeometric distribution:**

$$P(X=x) = P(x \text{ red}, \; d-x \text{ blue})$$

$$= \frac{\binom{\text{\# of ways to pick } x \text{ red balls}}{\text{out of R red balls}} \binom{\text{\# of ways to pick } d-x \text{ blue balls}}{\text{out of B blue balls}}}{(\text{\# of ways to pick } d \text{ balls out of } R+B \text{ balls})} = \frac{\binom{R}{x}\binom{B}{d-x}}{\binom{R+B}{d}}$$

Here $\binom{a}{b} = \frac{a!}{b!\,(a-b)!}$, and $0 \le x \le R$, $0 \le d-x \le B$

The outcome of the draws can be displayed in a 2×2 table:

	Red	Blue	total
Drawn	X	$d - X$	d
Not Drawn	$R - X$	$B - (d - X)$	$R + B - d$
total	R	B	$R + B$

Note the **row and column totals** are both **fixed** in advance.

$$P(X = x) = \frac{\binom{R}{x}\binom{B}{d - x}}{\binom{R + B}{d}}$$

The hypergeometric probability above can be found by the command below.

```
dhyper(x, R, B, d)
```

where R = # of Red balls;
B = # of Blue balls;
d = # of draws;
x = # of Red balls obtained in d draws

Example: ECMO

Extracorporeal membrane oxygenation (ECMO) is a potentially life-saving procedure for treating newborn babies suffering from severe respiratory failure. An experiment[1] was conducted in which

- 29 babies were treated with ECMO and
- 10 babies treated with conventional medical therapy (CMT).

		Outcome		
		Die	Live	total
Treatment	ECMO	1	28	29
	CMT	4	6	10
	total	5	34	39

[1] Example 10.4.1 on p.412 in *Statistics for the Life Sciences* (5ed) by Samuels, Witmer, and Schaffner. Original study by O'Rourke et al. *Pediatrics*. 1989 Dec;84(6):957-63. PMID: 2685740. See also Ware, J. H. (1989). "Investigating Therapies of Potentially Great Benefit: ECMO". *Statistical Science*, 4(4), 298–306. http://www.jstor.org/stable/2245829

		Outcome		
		Die	Live	total
Treatment	ECMO			$n_{1+} = 29$
	CMT			$n_{2+} = 10$
	total			$n = 39$

H_0: Treatment and outcome are independent.
That is, ECMO is just as effective as CMT.

Suppose H_0 is true, and the experiment is started over in the same manner with 10 babies given CMT and 29 given ECMO. What would the two-way table be like?

		Outcome		
		Die	Live	total
Treatment	ECMO			$n_{1+} = 29$
	CMT			$n_{2+} = 10$
	total			$n = 39$

H_0: Treatment and outcome are independent.
That is, ECMO is just as effective as CMT.

Suppose H_0 is true, and the experiment is started over in the same manner with 10 babies given CMT and 29 given ECMO. What would the two-way table be like?

- Column sums $n_{+1} = 29$ and $n_{+2} = 10$ are fixed by the study design.

		Outcome		
		Die	Live	total
Treatment	ECMO	$n_{11} = ?$		$n_{1+} = 29$
	CMT			$n_{2+} = 10$
	total	$n_{+1} = 5$	$n_{+2} = 34$	$n = 39$

H_0: Treatment and outcome are independent.
That is, ECMO is just as effective than CMT.

- Under H_0, whether a baby can survive does not depend on whether he/she received CMT or ECMO. The 34 survivors will survive regardless of the treatment, and the remaining 5 are too ill to be saved by either treatment
  - Row sums $n_{1+} = 5$ and $n_{2+} = 34$ are fixed

		Outcome		
		Die	Live	total
Treatment	ECMO	$n_{11} = ?$		$n_{1+} = 29$
	CMT			$n_{2+} = 10$
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- Under H_0, whether a baby can survive does not depend on whether he/she received CMT or ECMO. The 34 survivors will survive regardless of the treatment, and the remaining 5 are too ill to be saved by either treatment
  - Row sums $n_{1+} = 5$ and $n_{2+} = 34$ are fixed
- As the row sums and column sums are fixed, once n_{11} is determined, the counts in the other 3 cells are also determined.

5 deaths (red balls)	34 survivors (blue balls)

↙ ↘

29 babies (balls) drawn at random received ECMO

n_{11} deaths, $29-n_{11}$ survivors

The remaining 10 babies received CMT

$5-n_{11}$ deaths, $10-(5-n_{11})$ survivors

Regarding the 5 deaths and 34 survivors as red balls and blue balls, the process of randomizing babies to treatments (29 to ECMO, 10 to CMT) is like drawing 29 balls (babies) at random to the ECMO group. Hence the number of deaths (red balls) in the ECMO group has a hypergeometric distribution:

$$P(n_{11} = i) = \frac{\binom{5}{i}\binom{34}{29-i}}{\binom{39}{29}}, \quad i = 0, 1, 2, 3, 4, 5$$

One-Sided Fisher's Exact Test (for 2×2 Tables)

H$_0$: independence

H$_a$: ECMO is more effective than CMT

	Die	Live	total
ECMO	1	28	29
CMT	4	6	10
total	5	34	39

Small n_{11} is evidence toward H$_a$.

The one-sided P-value is hence the **lower-tail** probability:

$$\begin{aligned} P\text{-value} &= \mathrm{P}(n_{11} \le n_{11}^{\text{obs}}) = \mathrm{P}(n_{11} \le 1) \\ &= \mathrm{P}(n_{11} = 0) + \mathrm{P}(n_{11} = 1) \\ &= \frac{\binom{5}{1}\binom{34}{28}}{\binom{39}{29}} + \frac{\binom{5}{0}\binom{34}{29}}{\binom{39}{29}} \approx 0.0106 + 0.0004 = 0.011 \end{aligned}$$

```
dhyper(0:1,5,34,29)
[1] 0.0004377 0.0105774
```

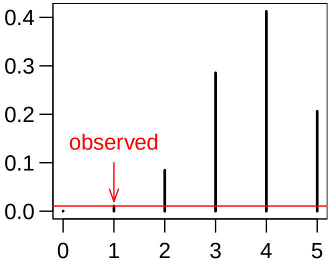
Two-Sided Fisher's Exact Test (for 2×2 Tables)

To test H_0: indep. v.s. H_a: ECMO & CMT are not equally effective, the **two-sided P-value** is the sum of all $P(n_{11} = k)$ such that

$$P(n_{11} = k) \le P(n_{11} = \text{the observed } n_{11})$$

For the ECMO data, $P(n_{11} = i) = \frac{\binom{5}{i}\binom{34}{28-i}}{\binom{39}{29}}$ for $i = 0, 1, 2, 3, 4, 5$ can be computed in R

```
> cbind(0:5, dhyper(0:5,5,34,29))
     [,1]      [,2]
[1,]    0 0.0004377
[2,]    1 0.0105774 <-- observed
[3,]    2 0.0846190
[4,]    3 0.2855892
[5,]    4 0.4125178
[6,]    5 0.2062589
```



Only $n_{11} = 1$ and $n_{11} = 0$ have probabilities below or equal to the probability of the observed $n_{11} = 1$.

The two-sided P-value is hence

$$\mathrm{P}(n_{11} = 1) + \mathrm{P}(n_{11} = 0) \approx 0.0106 + 0.0004 \approx 0.011,$$

which is identical to the one-sided P-value.

Conclusion: For both one-sided and two-sided test, ECMO is significantly better than CMT in saving babies' lives.

Two-Sided Fisher's Exact Test In R

```
ECMOdata = matrix(c(1, 4, 28, 6), nrow = 2,
    dimnames = list(Treatment = c("ECMO", "CMT"),
                    Outcome = c("Die", "Live")))
ECMOdata
         Outcome
Treatment Die Live
     ECMO   1   28
     CMT    4    6
```

Without any specification, R conducts a two-sided test.

```
fisher.test(ECMOdata)


    Fisher's Exact Test for Count Data


data:  ECMOdata
p-value = 0.011015
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
 0.0010592318 0.7318941336
```

One-Sided Fisher's Exact Test In R

Need to specify the direction of H_a in a one-sided test.

- `alternative="greater"` means the odds ratio is > 1
- `alternative="less"` means the odds ratio is < 1

Example (ECMO)

Small n_{11} is evidence for the H_a of ECMO being more effective, which implies OR < 1.

	Die	Live
ECMO	1	28
CMT	4	6

```
fisher.test(ECMOdata, alternative="less")


    Fisher's Exact Test for Count Data


data:  ECMOdata
p-value = 0.011015
alternative hypothesis: true odds ratio is less than 1
95 percent confidence interval:
 0.00000000 0.54535104
sample estimates:
```

Fisher's Exact Tests for 2×2 Tables

Under H_0: X & Y are independent, the exact null distribution of n_{11} is the **hypergeometric distribution**:

	$Y = 1$	$Y = 2$	sum
$X = 1$	n_{11}	n_{12}	n_{1+}
$X = 2$	n_{21}	n_{22}	n_{2+}
sum	n_{+1}	n_{+2}	n

$$P(n_{11}) = \frac{\binom{n_{+1}}{n_{11}}\binom{n_{+2}}{n_{12}}}{\binom{n}{n_{1+}}}$$

or

	$Y = 1$	$Y = 2$	sum
$X = 1$	n_{11}	n_{12}	n_{1+}
$X = 2$	n_{21}	n_{22}	n_{2+}
sum	n_{+1}	n_{+2}	n

$$P(n_{11}) = \frac{\binom{n_{1+}}{n_{11}}\binom{n_{2+}}{n_{21}}}{\binom{n}{n_{+1}}}$$

Fisher's Exact Tests for 2×2 Tables

Under H_0: X & Y are independent, the exact null distribution of n_{11} is the **hypergeometric distribution**:

	Y = 1	Y = 2	sum
X = 1	n_{11}	n_{12}	n_{1+}
X = 2	n_{21}	n_{22}	n_{2+}
sum	n_{+1}	n_{+2}	n

$$P(n_{11}) = \frac{\binom{n_{+1}}{n_{11}}\binom{n_{+2}}{n_{12}}}{\binom{n}{n_{1+}}}$$

or

	Y = 1	Y = 2	sum
X = 1	n_{11}	n_{12}	n_{1+}
X = 2	n_{21}	n_{22}	n_{2+}
sum	n_{+1}	n_{+2}	n

$$P(n_{11}) = \frac{\binom{n_{1+}}{n_{11}}\binom{n_{2+}}{n_{21}}}{\binom{n}{n_{+1}}}$$

Swapping Rows or Columns Doesn't Affect Hypergeometric Probabilities

	$Y = 1$	$Y = 2$	sum
$X = 1$	n_{11}	n_{12}	n_{1+}
$X = 2$	n_{21}	n_{22}	n_{2+}
sum	n_{+1}	n_{+2}	n

The two formulas on the previous page both equal to

$$P(n_{11}) = \frac{\binom{n_{+1}}{n_{11}}\binom{n_{+2}}{n_{12}}}{\binom{n}{n_{1+}}} = \frac{\binom{n_{1+}}{n_{11}}\binom{n_{2+}}{n_{21}}}{\binom{n}{n_{+1}}} = \frac{n_{1+}!\, n_{2+}!\, n_{+1}!\, n_{+2}!}{n!\, n_{11}!\, n_{12}!\, n_{21}!\, n_{22}!}.$$

Fisher's exact test treats the **rows and columns symmetrically**.

The formula is given for the n_{11} cell of the table. In fact, swapping the two rows or the two columns or exchanging X & Y doesn't affect the value of the hypergeometric probability.

Remarks About Fisher's Exact Test

- Fisher's exact test doesn't **distinguish between the explanatory and the response variables**, and hence can be applied to **both prospective and retrospective** studies
- Fisher's exact tests for $r \times c$ tables exist but are computationally intensive. See section 16.5 in [CDA].

Problem 2.23 Larynx Cancer Treatments (ICDA p.61)

	Cancer Controlled	Cancer Not Controlled	Total
Surgery	21	2	23
Radiation therapy	15	3	18
Total	36	5	41

Under H_0 of independence,

$$P(n_{11} = k) = \frac{\binom{23}{k}\binom{18}{36-k}}{\binom{41}{36}}$$

k	$23-k$	23
$36-k$	$k-18$	18
36	5	41

As $\binom{a}{b}$ is only defined when $0 \le b \le a$, k must satisfy

$$0 \le k \le 23, \quad 0 \le 36-k \le 18.$$

Thus, $P(n_{11} = k)$ is only defined when $k = 18, 19, 20, 21, 22, 23$.

Larynx Cancer Treatments — One-Sided P-value

To test H_0: indep. against

$$H_a\text{: surgery better than radiation therapy}$$

large values of n_{11} are evidence toward H_a, and hence the one-sided P-value is the upper tail probability

$$P(n_{11} \geq 21) = \sum_{k=21,22,23} \frac{\binom{23}{k}\binom{18}{36-k}}{\binom{41}{36}} \approx 0.38.$$

```
dhyper(21:23, 23, 18, 36)
[1] 0.275485123 0.093915383 0.011433177
sum(dhyper(21:23, 23, 18, 36))
[1] 0.38083368
```

Larynx Cancer Treatments — Two-Sided P-value

To test H_0: indep. against

H_a: surgery and radiation therapy are not equally effective

the **two-sided P-value** is the sum of all $P(n_{11} = k)$ such that

$$P(n_{11} = k) \leq P(n_{11} = n_{11}^{obs}) = P(n_{11} = 21)$$

```
cbind(18:23,dhyper(18:23, 23, 18, 36))
     [,1]    [,2]
[1,]   18 0.04490  <-- less than P(n11=21)
[2,]   19 0.21269  <-- less than P(n11=21)
[3,]   20 0.36157
[4,]   21 0.27549  <-- observed
[5,]   22 0.09392  <-- less than P(n11=21)
[6,]   23 0.01143  <-- less than P(n11=21)
```

Two-sided p-value is hence $P(n_{11} = 18, 19, 21, 22, 23) \approx 0.638$.

```
sum(dhyper(c(18,19,21,22,23), 23, 18, 36))
[1] 0.63842578
```

```
x = matrix(c(21, 2,15,3), byrow=T, nrow=2)
fisher.test(x,alternative="greater")

    Fisher's Exact Test for Count Data

data:  x
p-value = 0.38083
alternative hypothesis: true odds ratio is greater than 1
95 percent confidence interval:
 0.28648282        Inf
sample estimates:
odds ratio
  2.061731
```

```
fisher.test(x)  # two-sided


	Fisher's Exact Test for Count Data

data:  x
p-value = 0.63843
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
  0.20891152 27.55387471
sample estimates:
odds ratio
  2.061731
```