r x k tables

Blood type

Population	A	B	AB	O	
Florida	122	117	19	244	502
Iowa	1781	1351	289	3301	6721
Missouri	353	269	60	713	1395
	2256	1737	367	4258	8618

Question: Same distribution of blood types in each population?

Underlying probabilities

Observed data

	1	2	$\cdots$	k	
1	n_{11}	n_{12}	$\cdots$	n_{1k}	n_{1+}
2	n_{21}	n_{22}	$\cdots$	n_{2k}	n_{2+}
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\vdots$
r	n_{r1}	n_{r2}	$\cdots$	n_{rk}	n_{r+}
	n_{+1}	n_{+2}	$\cdots$	n_{+k}	n

Underlying probabilities

	1	2	$\cdots$	k	
1	p_{11}	p_{12}	$\cdots$	p_{1k}	p_{1+}
2	p_{21}	p_{22}	$\cdots$	p_{2k}	p_{2+}
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\vdots$
r	p_{r1}	p_{r2}	$\cdots$	p_{rk}	p_{r+}
	p_{+1}	p_{+2}	$\cdots$	p_{+k}	1

H_0: $p_{ij} = p_{i+} \times p_{+j}$ for all i,j

Expected counts

Observed data

	A	B	AB	O	
F	122	117	19	244	502
I	1781	1351	289	3301	6721
M	353	269	60	713	1395
	2256	1737	367	4258	8618

Expected counts

	A	B	AB	O	
F	131	101	21	248	502
I	1759	1355	286	3321	6721
M	365	281	59	689	1395
	2256	1737	367	4258	8618

Expected counts, under H_0: $e_{ij} = n_{i+} \times n_{+j}/n$ for all i,j

χ^2 statistic

Observed data

	A	B	AB	O	
F	122	117	19	244	502
I	1781	1351	289	3301	6721
M	353	269	60	713	1395
	2256	1737	367	4258	8618

Expected counts

	A	B	AB	O	
F	131	101	21	248	502
I	1759	1355	286	3321	6721
M	365	281	59	689	1395
	2256	1737	367	4258	8618

X^2 statistic = $\sum \frac{(\text{obs}-\text{exp})^2}{\text{exp}} = \cdots = 5.64$

Asymptotic approximation

If the sample size is large, the null distribution of the χ^2 and likelihood ratio test statistics will approximately follow a

$$\chi^2 \text{ distribution with } (r-1) \times (k-1) \text{ d.f.}$$

In the example, df = $(3-1) \times (4-1) = 6$

$$X^2 = 5.64 \quad \longrightarrow \quad P = 0.46.$$

Fisher's exact test

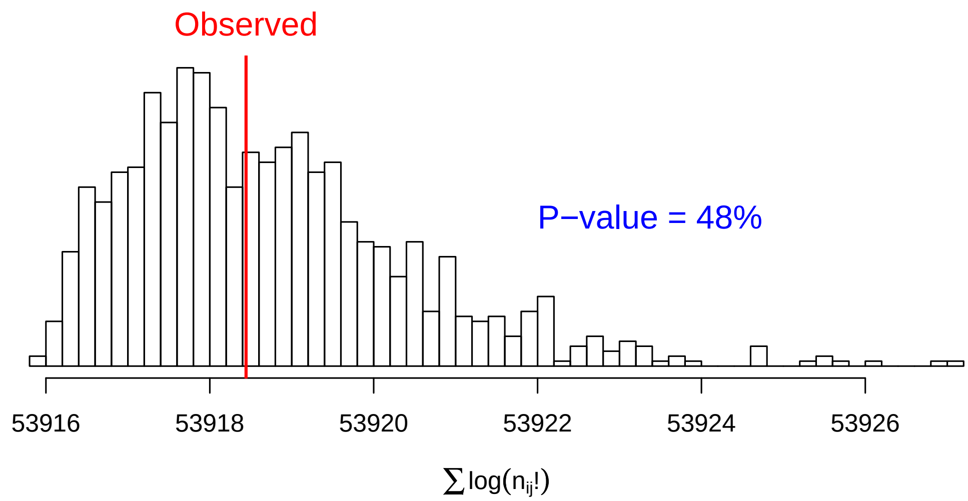
Observed data

	1	2	$\cdots$	k	
1	n_{11}	n_{12}	$\cdots$	n_{1k}	n_{1+}
2	n_{21}	n_{22}	$\cdots$	n_{2k}	n_{2+}
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\vdots$
r	n_{r1}	n_{r2}	$\cdots$	n_{rk}	n_{r+}
	n_{+1}	n_{+2}	$\cdots$	n_{+k}	n

- Assume H_0 is true.
- Condition on the marginal counts
- Then Pr(table) $\propto 1/\prod_{ij} n_{ij}!$

- Consider all possible tables with the observed marginal counts
- Calculate Pr(table) for each possible table.
- P-value = the sum of the probabilities for all tables having a probability equal to or smaller than that observed.

Fisher's exact test: The example



Since the number of possible tables can be very large, we often must resort to computer simulation.

Another example

Survival following treatment in five mouse strains

	Survive	
Strain	No	Yes
A	15	5
B	17	3
C	10	10
D	17	3
E	16	4

Question: Is the survival rate the same for all strains?

Results

Observed

Strain	Survive No	Survive Yes
A	15	5
B	17	3
C	10	10
D	17	3
E	16	4

Expected under H_0

Strain	Survive No	Survive Yes
A	15	5
B	15	5
C	15	5
D	15	5
E	15	5

$X^2 = 9.07 \longrightarrow P = 5.9\%$ [What is the df?]

Fisher's exact test: P = 8.7%

All pairwise comparisons

	N	Y	
A	15	5	⟶ P=69%
B	17	3	

	N	Y	
A	15	5	⟶ P=19%
C	10	10	

	N	Y	
A	15	5	⟶ P=69%
D	17	3	

	N	Y	
A	15	5	⟶ P=100%
E	16	4	

	N	Y	
B	17	3	⟶ P=4.1%
C	10	10	

	N	Y	
B	17	3	⟶ P=100%
D	17	3	

	N	Y	
B	17	3	⟶ P=100%
E	16	4	

	N	Y	
C	10	10	⟶ P=4.1%
D	17	3	

	N	Y	
C	10	10	⟶ P=9.6%
E	16	4	

	N	Y	
D	17	3	⟶ P=100%
E	16	4	

Is this a good thing to do?

Two-locus linkage in an intercross

	BB	Bb	bb
AA	6	15	3
Aa	9	29	6
aa	3	16	13

Are these two loci linked?

General test of independence

Observed data

	BB	Bb	bb
AA	6	15	3
Aa	9	29	6
aa	3	16	13

Expected counts

	BB	Bb	bb
AA	4.3	14.4	5.3
Aa	7.9	26.4	9.7
aa	5.8	19.2	7.0

χ^2 test: $X^2 = 10.4$ $\longrightarrow$ P = 3.5% [df = 4]

Fisher's exact test: P = 4.6%

A more specific test

Observed data

	BB	Bb	bb
AA	6	15	3
Aa	9	29	6
aa	3	16	13

Underlying probabilities

	BB	Bb	bb
AA	$\frac{1}{4}(1-\theta)^2$	$\frac{1}{2}\theta(1-\theta)$	$\frac{1}{4}\theta^2$
Aa	$\frac{1}{2}\theta(1-\theta)$	$\frac{1}{2}[\theta^2+(1-\theta)^2]$	$\frac{1}{2}\theta(1-\theta)$
aa	$\frac{1}{4}\theta^2$	$\frac{1}{2}\theta(1-\theta)$	$\frac{1}{4}(1-\theta)^2$

H_0: $\theta = 1/2$ versus H_a: $\theta < 1/2$

$\longrightarrow$ Use a “likelihood ratio test” (LRT).

- Obtain the general MLE of θ.
- Calculate the LRT statistic = 2 ln $\left\{ \frac{\Pr(\text{data} \mid \hat{\theta})}{\Pr(\text{data} \mid \theta{=}1/2)} \right\}$
- Compare this statistic to a $\chi^2(\text{df} = 1)$.

Results

	BB	Bb	bb
AA	6	15	3
Aa	9	29	6
aa	3	16	13

MLE: $\hat{\theta}$ = 0.359

LRT statistic: LRT = 7.74 $\longrightarrow$ P = 0.54% [df = 1]

- Here we assume Mendelian segregation, and that deviation from H_0 is “in a particular direction.”
- If these assumptions are correct, we’ll have greater power to detect linkage using this more specific approach.

Sample size determination

$\longrightarrow$ We seek to demonstrate that strains A and B differ in their survival rates following treatment.

How many mice from each group to study?

Generally, our goal is to have 80% power to detect a “meaningful” difference.

Power depends on. . .

- Structure of the experiment
- Method of analysis
- Sample size
- Chosen significance level (α)
- The underlying truth

We usually seek to determine the sample size that will give us 80% power to detect the smallest difference that we consider meaningful.

Calculating power

To determine power, we need:

1. The null distribution of the test statistic (so that we can determine the appropriate critical value).
2. The distribution of the test statistic under the alternative hypothesis.

For the t-test, there were analytical formulas for these.

For testing independence in a 2 x 2 table, we must resort to computer simulation.

Power in 2 x 2 tables

Suppose we assay 20 individuals from each strain.

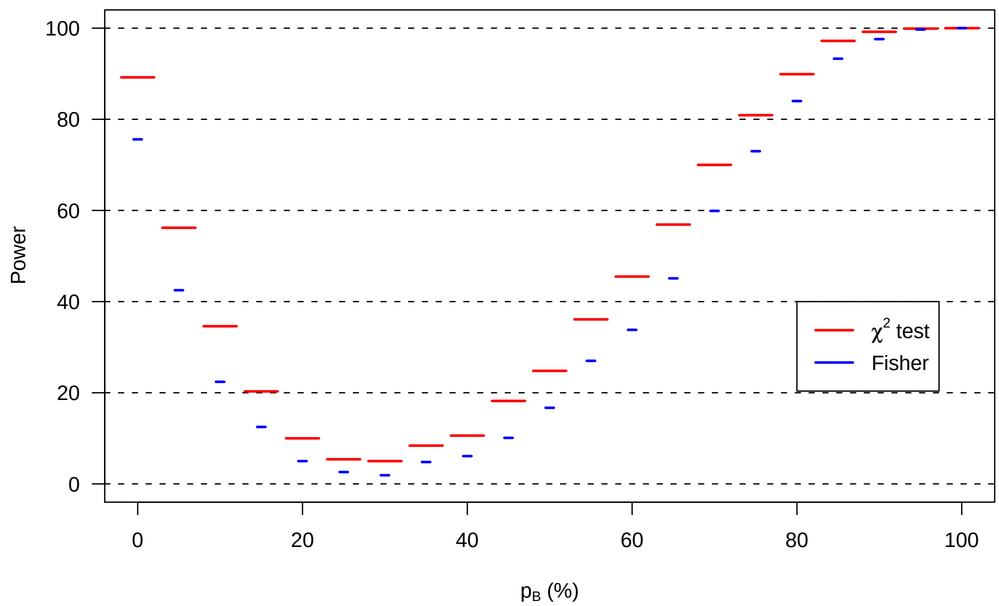
Let p_A = Pr(survive treatment | strain A) and
p_B = Pr(survive treatment | strain B).

To estimate power:

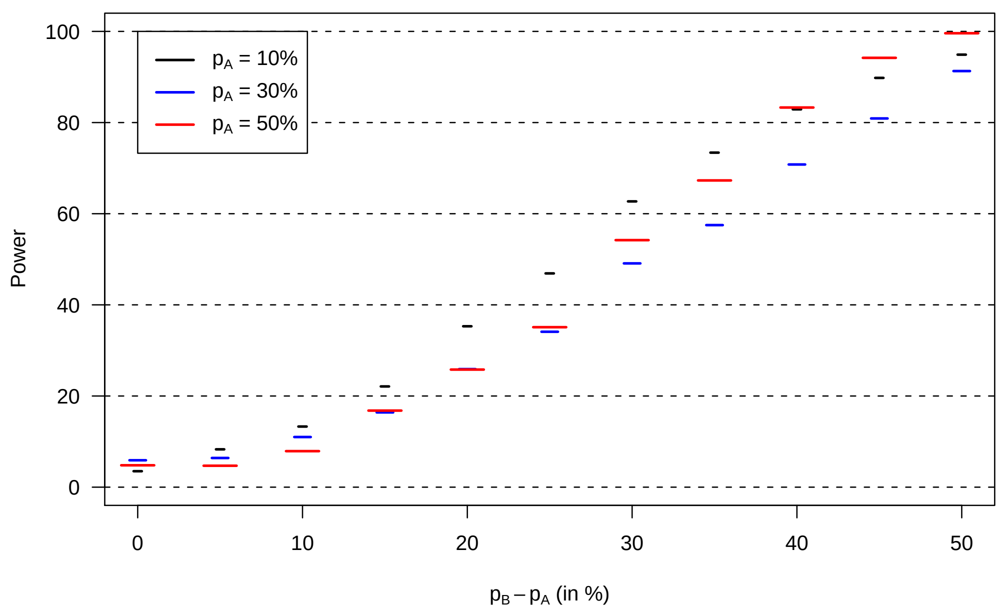
1. Simulate data for some specified p_A and p_B.
2. Calculate the chosen test statistic.
3. Calculate the corresponding P-value.
4. Repeat 1–3 many times (say 250).
5. The estimated power = prop'n of P-values $\leq$ 0.05

Power in 2 x 2 tables

The case n=20 per group and p_A = 30%.
[results based on 10,000 simulations]

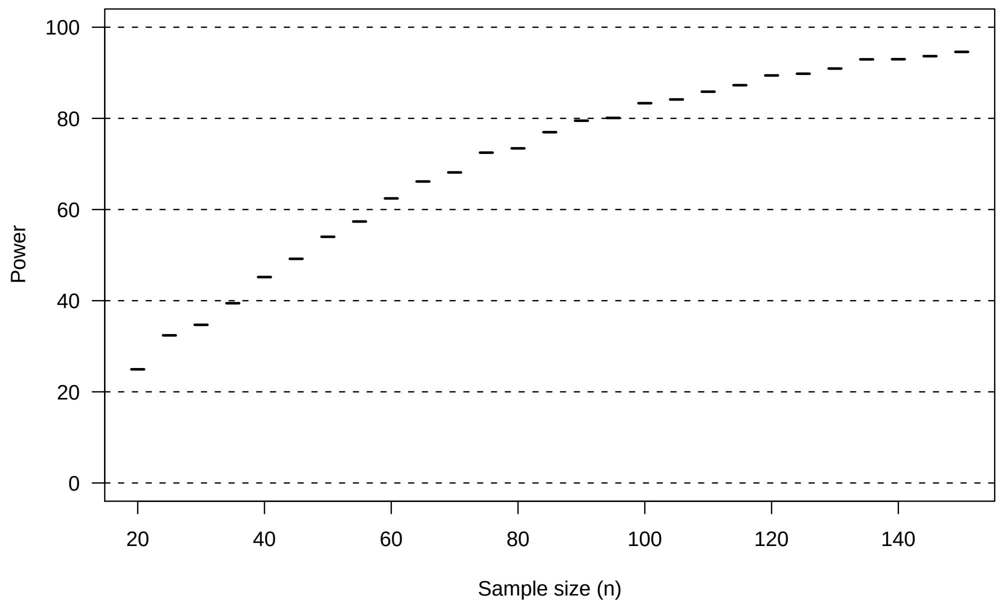


Power of χ^2 test



To get the sample size. . .

Results χ^2 test for p_A = 30% and p_B = 50%.



Notes

- There are formulas available for all sorts of different statistical tests and experimental situations.
- Simulations are time-consuming (and require programming), but can be used in virtually any situation.
- 250 simulation replicates is usually enough to get a good estimate of power, but for making power comparisons between different statistical methods, many more replicates are often necessary.
- Power is an important criterion in choosing between different statistical tests (such as the χ^2 test versus Fisher's exact test).

Another example

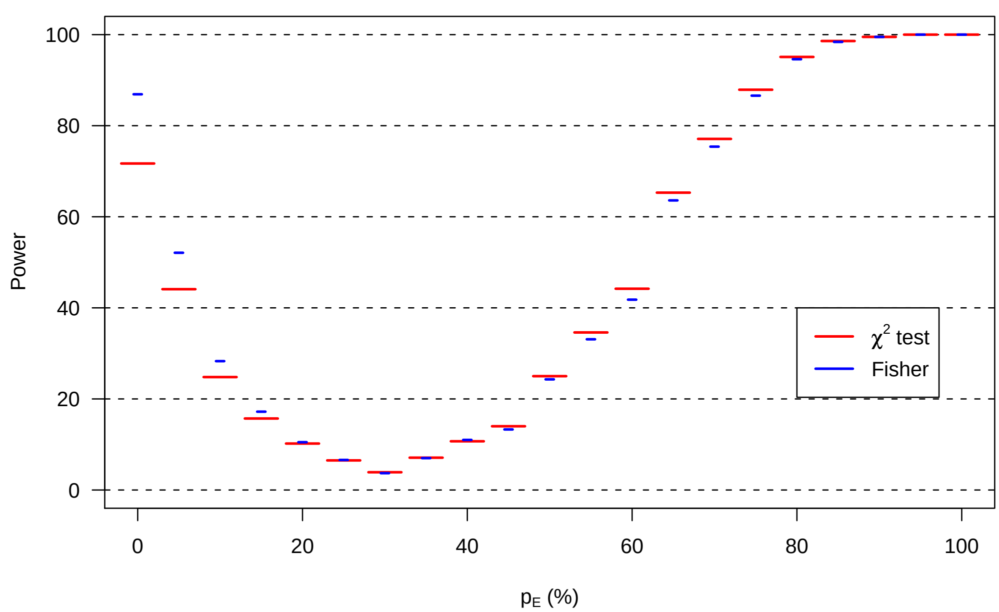
	N	Y
A		
B		
C		
D		
E		

- Survival following treatment in 5 mouse strains.
- Seek to demonstrate that the strains differ.
- Power for the case of 20 individuals per strain?

- We might focus on the case that strains A–D are the same, but strain E is different (the worst possible case).
- We must then specify Let p_A = Pr(survive treatment | strain A) and p_E = Pr(survive treatment | strain E).

Power for this example

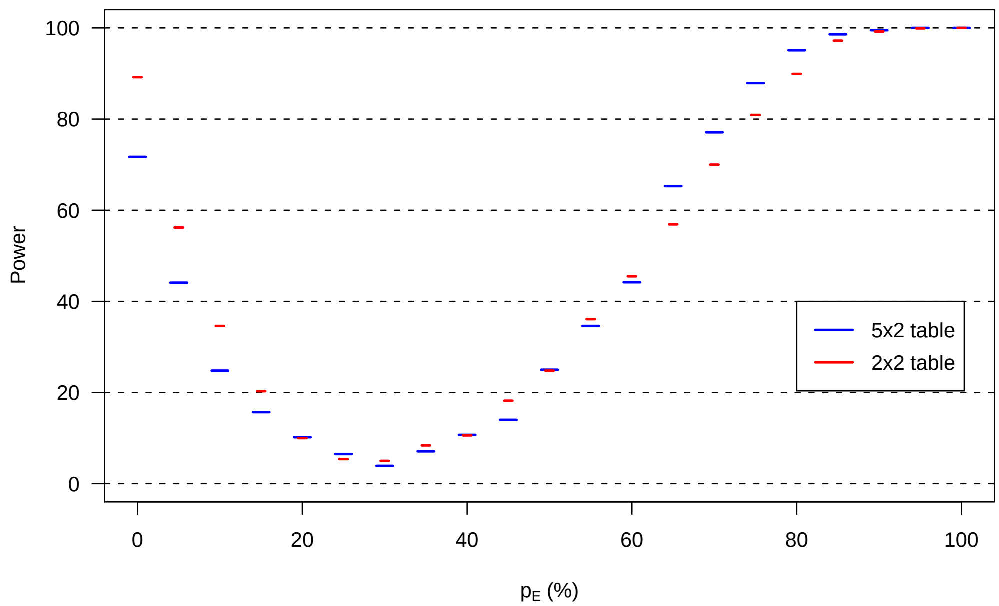
The case n=20 per group, and $p_A = p_B = p_C = p_D = 30\%$.



Comparison to 2 x 2 table

Comparing all 5 strains versus comparing just strains A and E.

(Considering just the χ^2 test.)



Final points

- Assumptions underlying tests in contingency tables:
  1. Data are a random sample from some population or populations.
     - Two or more independent samples observed with respect to one variable
     - One random sample observed with respect to two variables.
  2. Observations within a sample are independent.
- Ordinal data may require different techniques

	None	Some	A lot
A			
B			