Fisher's Exact Test

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There are many ways to evaluate whether a sample is different from another one. The use of one test or another mainly depends on the data we want to compare. For instance, one of these evaluation tools is the Fisher's Exact Test, which is used when comparing categorical data that can be structured as a contingency table, that is, two different groups compared because they express a different characteristic (e.g., red/blue, recurrence/no recurrence).

	X_1	X_2	Total
Group 1	a	b	a+b
Group 2	c	d	c+d
Total	a+c	b+d	N = a+b+c+d

As it is an exact test, this test allows the calculation of the exact value for the significance of the deviation from the null hypothesis (i.e., the p-value). In this case, the Fisher's Exact Test is based on the hypergeometric distribution, which can be described as follows:

$$P(X = r) = \frac{\binom{K}{r}\binom{N-K}{n-r}}{\binom{N}{n}}$$

Where *X* is a random variable, *r* is the number of observed 'successes', *K* is the number of 'successes' in the whole population, *N* is the population size and *n* is the sample size.

We can understand the formula as the number of samples that can have the observed distribution (the order is not important) divided by all the possible sample combinations with that size. The first part of the dividend is related to the 'successes', while the second one is related to the 'failures'.

Following the nomenclature used in the contingency table, we get this formula:

$$p = \frac{\binom{a+c}{a}\binom{b+d}{b}}{\binom{N}{a+b}} = \frac{\binom{a+c}{a}\binom{b+d}{b}}{\binom{N}{b+d}} = \frac{\frac{(a+c)!}{a!\,c!} * \frac{(b+d)!}{b!\,d!}}{\frac{N!}{(a+b)!\,(c+d)!}}$$

$$\boldsymbol{p} = \frac{(\boldsymbol{a}+\boldsymbol{b})!\,(\boldsymbol{c}+\boldsymbol{d})!\,(\boldsymbol{a}+\boldsymbol{c})!\,(\boldsymbol{b}+\boldsymbol{d})!}{\boldsymbol{a}!\,\boldsymbol{b}!\,\boldsymbol{c}!\,\boldsymbol{d}!\,\boldsymbol{N}!}$$

Where $n! = n * (n-1) * (n-2) * \ldots * 1$ and $0! = 1$.

The values obtained from this formula are the exact probabilities for that specific conformation, so to obtain the p-value we would also need to calculate the probability of all combinations more extreme than the one studied (with lower probability), given the marginal totals. The sum of these probabilities will be the p-value.

To consider this p-value valid, we assume that:

- The samples are independent of each other.
- The subjects within each group are independent.
- Every subject is classified in only one category, not in more.
- The row and column totals are given, not random.

This test can be used with contingency tables of greater dimensions, but as its hand calculation is only feasible with 2x2 tables, in the practice it is only used in these cases. Additionally, in practice, this test is only used when the sample sizes are small and if any of the cells from the contingency table has a value below 5. When the sample is greater, the Chi-squared (χ2) test is used. The main difference of the χ2 test is that it is not an exact test, it is an approximation and is therefore inadequate when *n* is small.

Example

Let's now apply the Fisher Exact Test to an example from the following paper: Carender CN, Sekar P, Prasidthrathsint K, DeMik DE, Brown TS, Bedard NA (2022). Rates of Antimicrobial Resistance with Extended Oral Antibiotic Prophylaxis After Total Joint Arthroplasty. *Arthroplast Today*, 18, pp.112–8. https://doi.org/10.1016/j.artd.2022.09.007

In this paper, they compare the rate of antimicrobial resistance associated with extended oral antibiotic prophylaxis (EOAP) and the rate associated with the standard antibiotic prophylaxis (Std.). For coagulase-negative *Staphylococci* different from *S. epidermidis*, when treated with erythromycin (ERY), they obtained the following results:

	Non-susceptible	Susceptible	Total
EOAP	8	1	9
Std.	2	10	12
Total	10	11	21

We can calculate the probability of this conformation as follows:

$$p = \frac{9!\,12!\,10!\,11!}{8!\,1!\,2!\,10!\,21!} = 0.00168$$

In order to calculate the p-value, we need to calculate the probability of every conformation given those marginal totals and consider those probabilities lower than the one already calculated. The potential more extreme conformations are represented in the next table.

Conformation	Treatment	Non-susceptible	Susceptible	Total	p
1	EOAP	9	0	9	3.4E-5
	Std	1	11	12	
	Total	10	11	21	
2	EOAP	2	7	9	0.05052
	Std	8	4	12	
	Total	10	11	21	
3	EOAP	1	8	9	0.00561
	Std	9	3	12	
	Total	10	11	21	
4	EOAP	0	9	9	0.00019
	Std	10	2	12	
	Total	10	11	21	

Only the probability of conformations 1 and 4 is lower to the first probability, so we can discard the others. The p-value can be calculated as

$$pval = 0.00168 + 3.4 * 10^{-5} + 0.00019 = 0.00190$$

As this value is way lower than the threshold of 0.05 (noted as $P<0.01$ in the paper), we can reject the null hypothesis (EOAP-associated resistance rate is the same as Std-associated resistance rate) and conclude that the extended oral antibiotic prophylaxis with ERY increased resistance from coagulase-negative *Staphylococci* different from *S. epidermidis*.

Conclusions

The Fisher's Exact Test is a useful tool for the analyses of contingency tables and the calculation of exact p-values, especially when sample size is small. When larger samples are considered, approximated tests such as the Chi-squared test are used instead.

Bibliography and Recommended Links

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