

T-test

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1 Basic knowledge

$\phi(x)$ and $\Phi(x)$ are pdf and cdf of standard normal distribution, respectively. We use Z to represent a random variable that follows standard normal distribution and z_α the lower α quantile of standard normal distribution. Therefore

$$P(Z \leq z_\alpha) = \Phi(z_\alpha) = \alpha.$$

Theorem 1. Let x_1, \dots, x_n be a random sample from a population with mean μ and variance $\sigma^2 < \infty$. Then

1. $E\bar{x} = \mu$.
2. $\text{Var}\bar{x} = \sigma^2/n$.
3. $ES^2 = \sigma^2$, where $S^2 = \frac{1}{n-1} \sum_{i=1}^n (x_i - \bar{x})^2$.

Theorem 2. Let x_1, \dots, x_n be a random sample from $N(\mu, \sigma^2)$. Then

1. $\bar{X} \sim N(\mu, \sigma^2/n)$.
2. \bar{X} is independent of S^2 .
3. $(n-1)S^2/\sigma^2$ follows a chi-squared distribution with $n-1$ degree of freedom.

2 One-sample test

Consider a random sample x_1, \dots, x_n from $N(\mu, \sigma^2)$. The likelihood is

$$\begin{aligned} f(x_1, \dots, x_n) &= \prod_{i=1}^n (2\pi\sigma^2)^{-1/2} \exp\left(-\frac{(x_i - \mu)^2}{2\sigma^2}\right) \\ &= (2\pi\sigma^2)^{-n/2} \exp\left(-\frac{\sum_{i=1}^n (x_i - \mu)^2}{2\sigma^2}\right). \end{aligned}$$

We propose the test

$$H_0 : \mu = \mu_0 \quad \text{v.s.} \quad H_1 : \mu \neq \mu_0$$

2.1 variance known

Construct LRT

$$LR = \frac{\max_{\mu \in H_0} f(x_1, \dots, x_n | \mu)}{\max_{\mu \in H_0 \cup H_1} f(x_1, \dots, x_n | \mu)} = \frac{f(x_1, \dots, x_n | \mu = \mu_0)}{f(x_1, \dots, x_n | \mu = \bar{x})} = \exp\left(-\frac{(\bar{x} - \mu_0)^2}{2\sigma^2/n}\right)$$

Therefore rejecting H_0 when LR is smaller than some constant C is equivalent to rejecting H_0 when $|\bar{x} - \mu_0|$ is larger than some other constant C . Hence

$$\text{Reject Region: } \{\bar{x} : |\bar{x} - \mu_0| > C\}$$

2.2 variance unknown

When σ^2 is unknown, the MLE under H_0 is

$$\mu_{(0)} = \mu_0, \quad \sigma_{(0)}^2 = \frac{1}{n} \sum_{i=1}^n (x_i - \mu_0)^2.$$

And the MLE under $H_0 \cup H_1$ is

$$\mu_{(0 \cup 1)} = \bar{x}, \quad \sigma_{(0 \cup 1)}^2 = \frac{1}{n} \sum_{i=1}^n (x_i - \bar{x})^2.$$

Note: MLE for σ^2 offers smaller MSE than S^2 , but it's biased.

Then the likelihood ratio is

$$LR = \frac{f(x_1, \dots, x_n | \mu = \mu_{(0)}, \sigma^2 = \sigma_{(0)}^2)}{f(x_1, \dots, x_n | \mu = \mu_{(0 \cup 1)}, \sigma^2 = \sigma_{(0 \cup 1)}^2)} = \frac{\left(\sum_{i=1}^n (x_i - \mu_0)^2\right)^{-n/2}}{\left(\sum_{i=1}^n (x_i - \bar{x})^2\right)^{-n/2}} \propto \frac{\left(\sum_{i=1}^n (\bar{x} - \mu_0)^2\right)^{-n/2}}{\left(\sum_{i=1}^n (x_i - \bar{x})^2\right)^{-n/2}},$$

where for the last part we mainly focus on terms related to μ_0 . So to reject H_0 when LR is small is equivalent to

$$\text{Reject Region: } \left\{ \bar{x} : \frac{|\bar{x} - \mu_0|}{\sqrt{\sum_{i=1}^n (x_i - \bar{x})^2}} > C \right\}$$

The idea is similar to that in Section 2.1. But we replace σ^2 with S^2 .

3 Two sample test

Consider two random samples $x_1, \dots, x_{n_1} \sim N(\mu_1, \sigma_1^2)$ and $y_1, \dots, y_{n_2} \sim N(\mu_2, \sigma_2^2)$. Then the likelihood of the data is

$$\begin{aligned} & f(x_1, \dots, x_{n_1}, y_1, \dots, y_{n_2} | \mu_1, \mu_2, \sigma_1^2, \sigma_2^2) \\ &= (2\pi\sigma_1^2)^{-n_1/2} (2\pi\sigma_2^2)^{-n_2/2} \exp \left(-\frac{\sum_{i=1}^{n_1} (x_i - \mu_1)^2}{2\sigma_1^2} - \frac{\sum_{i=1}^{n_2} (y_i - \mu_2)^2}{2\sigma_2^2} \right) \\ &= \end{aligned}$$

We propose the test

$$H_0 : \mu_1 = \mu_2 \quad \text{v.s.} \quad H_1 : \mu_1 \neq \mu_2.$$

3.1 Two-sample, variance known

When σ_1^2 and σ_2^2 are known, the likelihood satisfies

$$f(x_1, \dots, x_{n_1}, y_1, \dots, y_{n_2} | \mu_1, \mu_2) \propto \exp \left(-\frac{n_1 (\bar{x} - \mu_1)^2}{2\sigma_1^2} - \frac{n_2 (\bar{y} - \mu_2)^2}{2\sigma_2^2} \right).$$

Therefore under H_0 , the MLE for μ_1 and μ_2 is

$$\mu_{1(0)} = \mu_{2(0)} = \mu_{(0)} = \frac{\sigma_2^2 n_1 \bar{x} + \sigma_1^2 n_2 \bar{y}}{\sigma_2^2 n_1 + \sigma_1^2 n_2}.$$

And under $H_0 \cup H_1$, the MLE for μ_1 and μ_2 is

$$\mu_{1(0 \cup 1)} = \bar{x}, \quad \mu_{2(0 \cup 1)} = \bar{y}.$$

Then the likelihood ratio is

$$\begin{aligned} LR &= \frac{\max_{H_0} f(\mathbf{x}, \mathbf{y} | \mu_1, \mu_2)}{\max_{H_0 \cup H_1} f(\mathbf{x}, \mathbf{y} | \mu_1, \mu_2)} \\ &= \frac{f(\mathbf{x}, \mathbf{y} | \mu_1 = \mu_2 = \mu_{(0)})}{f(\mathbf{x}, \mathbf{y} | \mu_1 = \mu_{1(0 \cup 1)}, \mu_2 = \mu_{2(0 \cup 1)})} \\ &\propto \exp \left(-\frac{1}{2} \left(\frac{n_1 (\bar{x} - \mu_{(0)})^2}{\sigma_1^2} + \frac{n_2 (\bar{y} - \mu_{(0)})^2}{\sigma_2^2} \right) \right) \\ &= \exp \left(-\frac{1}{2} \frac{n_1 n_2}{\sigma_2^2 n_1 + \sigma_1^2 n_2} (\bar{x} - \bar{y})^2 \right). \end{aligned}$$

From the idea of LRT, H_0 is rejected when LR is small enough, which means the reject rule is

$$\text{Reject Region: } \{(\bar{x}, \bar{y}) | |\bar{x} - \bar{y}| > C\}$$

3.2 Two-sample, variance unknown but equal

When σ_1 and σ_2 are both unknown but equal, denoted by σ . The likelihood of the data becomes

$$f(x_1, \dots, x_{n_1}, y_1, \dots, y_{n_2} | \mu_1, \mu_2, \sigma^2) \\ = (2\pi\sigma^2)^{-n_1/2-n_2/2} \exp\left(-\frac{\sum_{i=1}^{n_1} (x_i - \mu_1)^2 + \sum_{i=1}^{n_2} (y_i - \mu_2)^2}{2\sigma^2}\right).$$

So the MLE under H_0 is

$$\mu_{1(0)} = \mu_{2(0)} = \mu_{(0)} = \frac{n_1\bar{x} + n_2\bar{y}}{n_1 + n_2}, \quad \sigma_{(0)}^2 = \frac{\sum_{i=1}^{n_1} (x_i - \mu_{(0)})^2 + \sum_{i=1}^{n_2} (y_i - \mu_{(0)})^2}{n_1 + n_2}$$

And the MLE under $H_0 \cup H_1$ is

$$\mu_{1(0 \cup 1)} = \bar{x}, \quad \mu_{2(0 \cup 1)} = \bar{y}, \quad \sigma_{(0 \cup 1)}^2 = \frac{\sum_{i=1}^{n_1} (x_i - \bar{x})^2 + \sum_{i=1}^{n_2} (y_i - \bar{y})^2}{n_1 + n_2}.$$

Then the likelihood ratio is

$$LR = \frac{f(\mathbf{x}, \mathbf{y} | \mu_1 = \mu_2 = \mu_{(0)}, \sigma^2 = \sigma_{(0)}^2)}{f(\mathbf{x}, \mathbf{y} | \mu_1 = \mu_{1(0 \cup 1)}, \mu_2 = \mu_{2(0 \cup 1)}, \sigma^2 = \sigma_{(0 \cup 1)}^2)} \\ = \left(\frac{\sigma_{(0)}^2}{\sigma_{(0 \cup 1)}^2} \right)^{-n_1/2-n_2/2} \\ = \left(\frac{\sum_{i=1}^{n_1} (x_i - \bar{x} + \bar{x} - \mu_{(0)})^2 + \sum_{i=1}^{n_2} (y_i - \bar{y} + \bar{y} - \mu_{(0)})^2}{\sum_{i=1}^{n_1} (x_i - \bar{x})^2 + \sum_{i=1}^{n_2} (y_i - \bar{y})^2} \right)^{-n_1/2-n_2/2} \\ = \left(1 + \frac{n_1 (\bar{x} - \mu_{(0)})^2 + n_2 (\bar{y} - \mu_{(0)})^2}{\sum_{i=1}^{n_1} (x_i - \bar{x})^2 + \sum_{i=1}^{n_2} (y_i - \bar{y})^2} \right)^{-n_1/2-n_2/2} \\ = \left(1 + \frac{n_1 n_2}{n_1 + n_2} \cdot \frac{(\bar{x} - \bar{y})^2}{\sum_{i=1}^{n_1} (x_i - \bar{x})^2 + \sum_{i=1}^{n_2} (y_i - \bar{y})^2} \right)^{-n_1/2-n_2/2}.$$

So to reject H_0 when the likelihood ratio is small enough implies that the reject region is

$$\text{Reject region: } \left\{ (\mathbf{x}, \mathbf{y}) \left| \frac{|\bar{x} - \bar{y}|}{\sqrt{\sum_{i=1}^{n_1} (x_i - \bar{x})^2 + \sum_{i=1}^{n_2} (y_i - \bar{y})^2}} > C \right. \right\}.$$

3.2.1 Regional consistency

We assume there's no difference in regional and global efficacy, which means

$$\begin{aligned}x_{r,1}, \dots, x_{r,n_{r,1}} &\sim N(\mu_1, \sigma^2) \\x_{o,1}, \dots, x_{o,n_{o,1}} &\sim N(\mu_1, \sigma^2) \\y_{r,1}, \dots, y_{r,n_{r,2}} &\sim N(\mu_2, \sigma^2) \\y_{o,1}, \dots, y_{o,n_{o,2}} &\sim N(\mu_2, \sigma^2)\end{aligned}$$

where r and o stand for 'region' and 'other' and clearly we have

$$n_{r,1} + n_{o,1} = n_1, \quad n_{r,2} + n_{o,2} = n_2$$

For regional and global summary, we have

$$\begin{aligned}\bar{x}_r &\sim N(\mu_1, \sigma^2/n_{r,1}) \\ \bar{x}_o &\sim N(\mu_1, \sigma^2/n_{o,1}) \\ \bar{y}_r &\sim N(\mu_2, \sigma^2/n_{r,2}) \\ \bar{y}_o &\sim N(\mu_2, \sigma^2/n_{o,2})\end{aligned}$$

and

$$\begin{aligned}\bar{x} &= \frac{n_{r,1}}{n_{r,1} + n_{o,1}} \bar{x}_r + \frac{n_{o,1}}{n_{r,1} + n_{o,1}} \bar{x}_o \sim N(\mu_1, \sigma^2/n_1) \\ \bar{y} &= \frac{n_{r,2}}{n_{r,2} + n_{o,2}} \bar{y}_r + \frac{n_{o,2}}{n_{r,2} + n_{o,2}} \bar{y}_o \sim N(\mu_2, \sigma^2/n_2)\end{aligned}$$

And the treatment effect summary follows

$$\begin{aligned}\Delta_r &= \bar{x}_r - \bar{y}_r \sim N\left(\mu_1 - \mu_2, \left(\frac{1}{n_{r,1}} + \frac{1}{n_{r,2}}\right) \sigma^2\right) \\ \Delta_c &= \bar{x}_o - \bar{y}_o \sim N\left(\mu_1 - \mu_2, \left(\frac{1}{n_{o,1}} + \frac{1}{n_{o,2}}\right) \sigma^2\right)\end{aligned}$$

And

$$\begin{aligned}\Delta &= \bar{x} - \bar{y} \sim N\left(\mu_1 - \mu_2, \left(\frac{1}{n_1} + \frac{1}{n_2}\right) \sigma^2\right) \\ &= \frac{n_{r,1}}{n_{r,1} + n_{o,1}} \bar{x}_r + \frac{n_{o,1}}{n_{r,1} + n_{o,1}} \bar{x}_o - \left(\frac{n_{r,2}}{n_{r,2} + n_{o,2}} \bar{y}_r + \frac{n_{o,2}}{n_{r,2} + n_{o,2}} \bar{y}_o \right)\end{aligned}$$

But unfortunately, Δ can NOT be easily break into Δ_r and Δ_o . Now, let's first assume there's a fixed ratio between the two arms, both in region and other areas, which means

$$n_{r,1} = kn_{r,2}, \quad n_{o,1} = kn_{o,2}$$

Then

$$\begin{aligned}\Delta_r &\sim N\left(\mu_1 - \mu_2, \frac{1+k}{n_{r,1}} \sigma^2\right) \\ \Delta_o &\sim N\left(\mu_1 - \mu_2, \frac{1+k}{n_{r,2}} \sigma^2\right) \\ \Delta &= \frac{n_{r,1}}{n_{r,1} + n_{o,1}} \Delta_r + \frac{n_{o,1}}{n_{r,1} + n_{o,1}} \Delta_o \sim N\left(\mu_1 - \mu_2, \frac{1+k}{n_1} \sigma^2\right)\end{aligned}$$

Considering the show trend criteria 'Method 1', which is regional treatment improvement keeps certain percentage of global treatment improvement, that is to say for some fixed POSITIVE ρ , it's required that

$$\Delta_r \geq \rho\Delta$$

as a 'show trend criteria'. Then marginally, we have the show trend probability

$$\begin{aligned} P(\Delta_r \geq \rho\Delta) &= P\left(\Delta_r \geq \rho\left(\frac{n_{r,1}}{n_{r,1} + n_{o,1}}\Delta_r + \frac{n_{o,1}}{n_{r,1} + n_{o,1}}\Delta_o\right)\right) \\ &= P\left(\frac{n_{r,1} - \rho n_{r,1} + n_{o,1}}{n_{r,1} + n_{o,1}}\Delta_r \geq \frac{\rho n_{o,1}}{n_{r,1} + n_{o,1}}\Delta_o\right) \end{aligned}$$

which can be easily calculated since Δ_r and Δ_o are independent with known distribution.

3.3 Two-sample, variance unknown and unequal

For this we refer to the "Welch's unequal variance t-test" [WELCH, 1947]. The test statistic is

$$t = \frac{\bar{x} - \bar{y}}{s_{\bar{\Delta}}},$$

where

$$s_{\bar{\Delta}} = \sqrt{\frac{s_x^2}{n_1} + \frac{s_y^2}{n_2}}.$$

Here $s_x^2 = \frac{1}{n_1-1} \sum_{i=1}^{n_1} (x_i - \bar{x})^2$ and $s_y^2 = \frac{1}{n_2-1} \sum_{i=1}^{n_2} (y_i - \bar{y})^2$ are the unbiased estimator for σ_1^2 and σ_2^2 . The test statistic approximately follows a t-distribution with degree of freedom being

$$\text{d.f.} = \frac{\left(\frac{s_x^2}{n_1} + \frac{s_y^2}{n_2}\right)^2}{\frac{(s_x^2/n_1)^2}{n_1-1} + \frac{(s_y^2/n_2)^2}{n_2-1}}.$$

References

B. L. WELCH. THE GENERALIZATION OF 'STUDENT's' PROBLEM WHEN SEVERAL DIFFERENT POPULATION VARIANCES ARE INVOLVED. *Biometrika*, 34 (1-2):28–35, 1947. doi: 10.1093/biomet/34.1-2.28.