Biostatistics

O.O.Bogomolets National Medical University

March 18, 2013

Contents

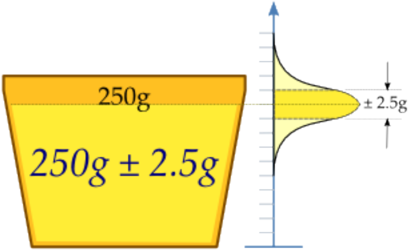
- Confidence intervals
- Evidence-based medicine
- Clinical trials
- Hypothesis testing

Confidence intervals

Definition

$$\Pr_{\theta}(u(X) < \theta < v(X)) = \gamma \ \forall\theta.$$

- θ – *statistical parameter, which is a quantity to be estimated*
- γ – *confidence level*



Chebyshev's inequality

- $$P(|X-\mu| \geq k\sigma) \leq \frac{1}{k^2}$$
- The probability that a random variable lies beyond k standard deviations from its mean is less than $1/k^2$

$$\begin{array}{ccc} 2\sigma & \rightarrow & 25\% \\ 3\sigma & \rightarrow & 11\% \\ 4\sigma & \rightarrow & 6\% \end{array}$$

- This is not a bound, actual probability might be (much) smaller.

Chebyshev's inequality – example

- IQs are as a normal distribution with a μ of 100 and a σ 15
- What is the probability of a randomly drawn person having an IQ higher than 160 or below 40?
- Thus we want to know the probability of a person being more than 4 standard deviations from the mean
- Chebyshev's inequality suggests that this will be no larger than 6%
- The probability of a random draw from a bell curve being 4 standard deviations from the mean is on the order of 10^{-5} (one thousandth of one percent)

- Physists say, that they are "Six Sigma" sure that they've discovered Higg's boson
- Chebyshev's inequality states that the probability of a "Six Sigma" event(they have not observed most "popular" boson) is less than $1/6^2 \approx 3\%$
- If normal distribution for errors is assumed, the probability of a "six sigma" event is on the order of 10^{-9} (one ten millionth of a percent)

Confidence intervals

- Sample is from normal distribution
- We need CI for mean value
- Variance is not unknown

Example: we need to calculate CI for IQ level, hemoglobin, etc.

Confidence intervals

$\Phi(x) = \frac{1}{\sqrt{2\pi}} \int_0^x e^{\frac{-t^2}{2}} dt$

1. $$P(|\bar{x} - a| < \delta) = 2\Phi(t) = \gamma$$
2. Using CLT:

$$\delta = \frac{t\sigma}{\sqrt{n}} = tm, P(\bar{x} - \delta < a < \bar{x} + \delta) = 2\Phi(t) = \gamma$$

All we need to do is to find $t : \Phi(t) = \frac{\gamma}{2}$

Confidence intervals

- Sample is from normal distribution
- We need CI for mean value
- Variance is **unknown**

Student's t-distribution:

$$t = \frac{\xi_0}{\sqrt{\frac{1}{n}\sum_{i=1}^{n}\xi_i^2}}$$

Confidence intervals for the mean

- Notice that the t statistic is a pivot, therefore we use it to create a confidence interval for μ
- Let $t_{df,\alpha}$ be the α^{th} quantile of the t distribution with df degrees of freedom

$$
\begin{aligned}
& 1-\alpha \\
= \quad & P\left(-t_{n-1,1-\alpha/2} \leq \frac{\bar{X}-\mu}{S/\sqrt{n}} \leq t_{n-1,1-\alpha/2}\right) \\
= \quad & P\left(\bar{X} - t_{n-1,1-\alpha/2}S/\sqrt{n} \leq \mu \leq \bar{X} + t_{n-1,1-\alpha/2}S/\sqrt{n}\right)
\end{aligned}
$$

- Interval is $\bar{X} \pm t_{n-1,1-\alpha/2}S/\sqrt{n}$

Break

Let's have a **break**!

Evidence-based medicine

Definition

The use of mathematical estimates of the risk of benefit and harm, derived from high-quality research on population samples, to inform clinical decision-making in the diagnosis, investigation or management of individual patients

Why do we need it?

Ancient world	Modern days
facies Hippocratica	obesitas
Plague	Heart disease

Quality of evidence

Level I Evidence obtained from at least one properly designed randomized controlled trial.

Level II-1 Evidence obtained from well-designed controlled trials without randomization.

Level II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Statistical hypothesis testing

- A statistical hypothesis test is a method of making decisions using data
- A result is called **statistically significant** if it is unlikely to have occurred by chance alone, according to a pre-determined threshold probability, the **significance level**.
- A result that was found to be statistically significant is also called a **positive result**; conversely, a result whose probability under the null hypothesis exceeds the significance level is called a negative result or a null result.

Type I error and Type II error

	Null Hypothesis (H_0) is true	Alternative Hypothesis (H_1) is true
Fail to Reject Null Hypothesis	Right decision	Type II Error
Reject Null Hypothesis	Type I Error	Right decision

Statistical hypothesis testing

- We start with a research hypothesis of which the truth is unknown.
- The first step is to state the relevant null and alternative hypotheses. This is important as mis-stating the hypotheses will muddy the rest of the process.
- The second step is to consider the statistical assumptions being made about the sample in doing the test; for example, assumptions about the statistical independence or about the form of the distributions of the observations.
- Decide which test is appropriate, and stating the relevant test statistic.
- Derive the distribution of the test statistic under the null hypothesis from the assumptions.
- Compute from the observations the observed value tobs of the test statistic T.
- Decide to either fail to reject the null hypothesis or reject it in favor of the alternative.

1. $X, Y \sim N(\mu, \sigma^2)$.
2. $$H_0 : \mathrm{E}\, X \stackrel{d}{=} \mathrm{E}\, Y$$

Our "recipe":

1. $$Z = \frac{\bar{X} - \bar{Y}}{\sqrt{\frac{\sigma_X^2}{\nu_X} + \frac{\sigma_Y^2}{\nu_Y}}}$$
2. $\Phi(z) = \frac{1-\alpha}{2}$
3. If $|Z| < z$, H_0 is accepted.

1. $X, Y \sim N(\mu, \sigma^2)$.
2. $$H_0 : \mathrm{Var}\, X \overset{d}{=} \mathrm{Var}\, Y$$

Our “recipe”:

1. Calculate $\mathrm{Var}\, X$ and $\mathrm{Var}\, Y$
2. $FC = \frac{\max(\mathrm{Var}\, X, \mathrm{Var}\, Y)}{\min(\mathrm{Var}\, X, \mathrm{Var}\, Y)}$
3. Compare FC with Fisher distribution quantile with $\alpha/2$

Example

Control	Experiment
0,027	0,075
0,036	0,4
0,1	0,08
0,12	0,105
0,32	0,075
0,45	0,12
0,049	0,06
0,105	0,075

FC: $\frac{0{,}0232}{0{,}0128} = 1,8114$
Critical value for $2\alpha = 0.05$ $\nu_1 = \nu_2 = 7$ is 4,994

χ^2

- Suppose that S^2 is the sample variance from a collection of iid $N(\mu, \sigma^2)$ data; then
$$\frac{(n-1)S^2}{\sigma^2} \sim \chi^2_{n-1}$$
a Chi-squared distribution with $n-1$ degrees of freedom
- The Chi-squared distribution is skewed and has support on 0 to ∞
- The mean of the Chi-squared is its degrees of freedom
- The variance of the Chi-squared distribution is twice the degrees of freedom
$$\sum_{k=1}^{N} \frac{(\nu_k - np_k)^2}{np_i} \xrightarrow{d} \Xi^2_n$$

Pearson's χ^2 test

n – sample size.

:

1. We divide the entire range of values into small intervals $\{\Delta_k\}, k = 1, \dots N$

2. $$\chi_0^2 = \sum_{i=1}^{N} \frac{(v_i - np_i)^2}{np_i}$$

   $v_k = \sum_{j=1}^{n} I_{\{x_j \in \Delta_k\}}$ – frequency in Δ_k. $p_k = p\{x \in \Delta_k\}$ – probability of "getting into" Δ_k

3. $\nu = n - l - 1$.l –number of parameters

4. If $\chi_0^2 < \chi^2$, then H_0 is accepted.

Confidence interval for the variance

Note that if $\chi^2_{n-1,\alpha}$ is the α quantile of the Chi-squared distribution then

$$\begin{aligned} 1-\alpha &= P\left(\chi^2_{n-1,\alpha/2} \le \frac{(n-1)S^2}{\sigma^2} \le \chi^2_{n-1,1-\alpha/2}\right) \\ &= P\left(\frac{(n-1)S^2}{\chi^2_{n-1,1-\alpha/2}} \le \sigma^2 \le \frac{(n-1)S^2}{\chi^2_{n-1,\alpha/2}}\right) \end{aligned}$$

So that

$$\left[\frac{(n-1)S^2}{\chi^2_{n-1,1-\alpha/2}}, \frac{(n-1)S^2}{\chi^2_{n-1,\alpha/2}}\right]$$

is a $(1-\alpha)$ confidence interval for σ^2

Dixi