Global null testing

Modern Inference

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Acknowledgements

Much of the content was inspired by the following courses:

- Theory of Statistics by Prof. Emmanuel Cands
- Statistical methods for reproducibility by Prof. Aaditya Ramdas

and on a number of other sources.

Outline

1. **The p-value**
2. **Global null testing**
3. **Maximum statistic**
4. **Sum of statistics**
5. **Higher Criticism**

Deterministic proof by contradiction

1. Assume a proposition, the opposite of what you think about, i.e. the opposite conclusion of your theorem
2. Write down a sequence of logical steps/math
3. Derive a contradiction
4. Conclude that the proposition is false (which implies that the theorem is true)

Stochastic proof by contradiction

1. Set H_0 (the proposition)
2. Collect data (which is noisy)
3. Derive an apparent contradiction (i.e. if H_0 is true, then this data is very weird)
4. Hence we reject H_0; this is called a "discovery"

Hypothesis testing is stochastic because we might make errors: *Type I* (false discoveries) and *Type II* (missed discoveries)

Theorem: *There is no greatest even integer.*

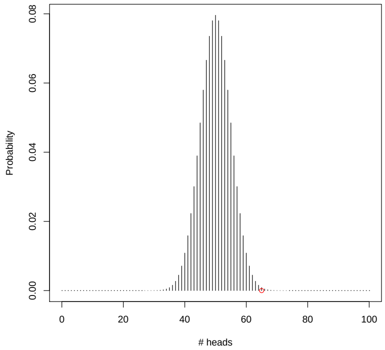
- We take the negation of the theorem and suppose it to be true: Suppose there is greatest even integer N. [We must deduce a contradiction.]
- Then, for every even integer n, $N \geq n$.
- Now suppose $M = N + 2$. Then, M is an even integer. [Because it is a sum of even integers.]
- Also, $M > N$ [since $M = N + 2$].
- Therefore, M is an integer that is greater than the greatest integer.
- This contradicts the supposition that $N \geq n$ for every even integer n. [Hence, the supposition is false and the statement is true.]

  And this completes the proof.

Assume we have a coin and want to determine whether or not it is fair. In this case we have

$$H_0 : \text{Coin is fair } (\theta = 1/2)$$
$$H_1 : \text{Coin is biased } (\theta \neq 1/2)$$

The probability distribution of $X =$ "the number of heads in 100 trials" under H_0 is Binomial($n = 100$, $\theta = 1/2$). After tossing the coin $n = 100$ times we then get $x = 65$ heads and $n - x = 35$ tails.



- Is this then enough to reject H_0?
- To determine this we calculate a *p*-value associated with our observed data assuming the null hypothesis
- A *p*-value is the probability of seeing what you saw - or something more extreme - given that H_0 is true.
- Small *p*-values imply an unexpected outcome, given that the null (H_0) is true
- So if $p = 0.0018$ then either H_0 isn't true or we are really unlucky and saw this data

The p-value

- Choose a test statistic $T = t(Y)$, large values of which cast doubts on H_0
- Observe the data y_{obs}, realization of Y
- $$p_{\mathrm{obs}} = \mathrm{P}_0(T \geq t_{\mathrm{obs}})$$

  where $t_{\mathrm{obs}} = t(y_{obs})$ and P_0 is the probability under H_0

p-value null distribution

- $p_{\mathrm{obs}} = 1 - F_0(t_{\mathrm{obs}})$, where F_0 is the null distribution function of T, supposed to be continuous and invertible.
- One interpretation of p_{obs} stems from the corresponding random variable $P = 1 - F_0(T)$
- The null distribution of P is *Uniform*(0,1): for any $u \in (0,1)$,

$$\mathrm{P}_0(P \leq u) = \mathrm{P}_0(F_0^{-1}(1-u) \leq T) = 1 - F_0(F_0^{-1}(1-u)) = u$$

One- and two-sided tests

- Suppose that we have a test statistic T with continuous distribution, small and large values of which indicate a departure from H_0
- Calculate

$$p_{\text{obs}}^{-} = \mathrm{P}_0(T \leq t_{\text{obs}}), \quad p_{\text{obs}}^{+} = \mathrm{P}_0(T \geq t_{\text{obs}})$$

- The p-value is

$$p_{\text{obs}} = 2\min(p_{\text{obs}}^{-}, p_{\text{obs}}^{+})$$

  This follows because the null distribution of $Q = \min(P^{-}, P^{+})$ is

$$Q = \min(1 - U(0,1), U(0,1)) = U(0, 1/2)$$

  thus the null distribution of $2Q$ is $U(0,1)$

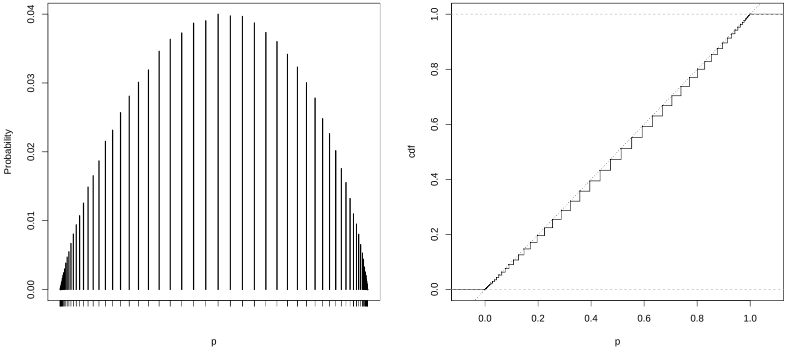
Discrete null distribution

- Suppose $T \sim \mathrm{Poisson}(\mu)$ and we observe $t_{\mathrm{obs}} = 3$
- We want to test $H_0 : \mu = 2$ vs $H_1 : \mu \neq 2$
- $$p^+_{\mathrm{obs}} = \mathrm{P}_0(T \geq t_{\mathrm{obs}}) = \sum_{t=t_{\mathrm{obs}}}^{\infty} \frac{\mu^t e^{-\mu}}{t!}$$

  $$p^-_{\mathrm{obs}} = \mathrm{P}_0(T \leq t_{\mathrm{obs}}) = \sum_{t=0}^{t_{\mathrm{obs}}} \frac{\mu^t e^{-\mu}}{t!}$$

  With discrete null distribution, p_{obs} is $q_{\mathrm{obs}} = \min(p^-_{\mathrm{obs}}, p^+_{\mathrm{obs}})$ plus the achievable p-value from the other tail of the distribution nearest to but not exceeding q_{obs}
- In the example, $p_{\mathrm{obs}} = 0.458 = \min(0.323, 0.857) + 0.135$

t	0	1	2	3	4	5
$\mathrm{P}_0(T \geq t)$	1	0.865	0.594	0.323	0.143	0.053
$\mathrm{P}_0(T \leq t)$	0.135	0.406	0.677	0.857	0.947	0.983



$\mathrm{P}_0(P = p)$ $\mathrm{P}_0(P \leq p)$

Example of null discrete distribution (pmf and cdf) of the *p*-value

Valid p-values

We have a *valid test* if the p-value is uniformly distributed under H_0, i.e.

$$\mathrm{P}_0(P \leq u) = u \quad \forall u \in (0,1)$$

or more generally (e.g. for discrete null distributions) if the p-value is *stochastically dominated* by the uniform distribution under H_0, i.e.

$$\mathrm{P}_0(P \leq u) \leq u \quad \forall u \in (0,1)$$

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3. Maximum statistic
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5. Higher Criticism

Inference on the mean

$$y \sim N_m(\mu, \Sigma)$$

where $y = (y_1, \ldots, y_m)^\mathsf{T}$ is the response, $\mu = (\mu_1, \ldots, \mu_m)^\mathsf{T}$ is the mean vector (where $\mu_i = 0$ means "no effect" and $\mu_i \neq 0$ means "effect") and Σ is the correlation matrix. Marginally, $y_i \sim N(\mu_i, 1)$

Consider the following questions:

1. *Detecting effects*: There is at least one μ_i different from 0?
2. *Counting effects*: How many μ_i are different from 0?
3. *Identifying effects*: Which μ_i are different from 0?

Global null

Testing the global null hypothesis aims at detecting any effect

$H_0 : \mu = 0$, i.e. $\mu_i = 0$ for all $i = 1, \dots, m$

$H_1 : \mu \neq 0$, i.e. $\mu_i \neq 0$ for at least one i

One-sided alternative

H_0: $\mu_i = 0$ for all $i = 1, \dots, m$

H_1: $\mu_i > 0$ for at least one i

We will consider three different tests (one-sided alternative):

- Maximum statistic: $T_{\max} = \max(y_1, \dots, y_m)$
- Sum of statistics $T_{\text{sum}} = \sum_{i=1}^m y_i$
- Higher criticism

For simplicity, assume that the y_is are independent (i.e. $\Sigma = I_m$)

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Maximum statistic

- The critical value $t_{1-\alpha}$ of the test based on the maximum statistic is
$$\mathrm{P}_0(T_{\max} \geq t_{1-\alpha}) = \alpha$$
where $t_{1-\alpha}$ is the $1-\alpha$ quantile of the distribution of the maximum of m independent standard normal variables
$$\int_{t_{1-\alpha}}^{\infty} m\phi(y)\Phi(y)^{m-1}dy = \alpha$$
where ϕ and Φ are the density and cdf of $N(0,1)$

Minimum p-value

- Equivalently, define $p_i = 1 - \Phi(y_i) \overset{H_0}{\sim} U(0,1)$ and use the minimum p-value

$$p_{\min} = \min(p_1, \ldots, p_m) \overset{H_0}{\sim} \mathrm{Beta}(1, m)$$

- The MinP test rejects H_0 if $p_{\min} \leq 1 - (1-\alpha)^{\frac{1}{m}}$
- To see this

$$\begin{aligned} \mathrm{P}_0(p_{\min} \leq 1 - (1-\alpha)^{\frac{1}{m}}) &= 1 - \mathrm{P}_0\Big(\bigcap_{i=1}^{m} \{p_i > 1 - (1-\alpha)^{\frac{1}{m}}\}\Big) \\ &= 1 - [(1-\alpha)^{\frac{1}{m}}]^m = \alpha \end{aligned}$$

Approximated critical value

- Replace $t_{1-\alpha}$ by $z_{1-\alpha/m}$, where z_α is the α quantile of $N(0,1)$

$$\begin{aligned} \mathrm{P}_0(T_{\max} \geq z_{1-\alpha/m}) &= \mathrm{P}_0\Big(\bigcup_{i=1}^{m}\{y_i \geq z_{1-\alpha/m}\}\Big) \\ &\leq \sum_{i=1}^{m} \mathrm{P}_0(y_i \geq z_{1-\alpha/m}) = m\frac{\alpha}{m} = \alpha \end{aligned}$$

- The union bound might seem crude, but with independent y_is the size of the test is very near α

$$\begin{aligned} \mathrm{P}_0(T_{\max} \geq z_{1-\alpha/m}) &= 1 - \prod_{i=1}^{m} \mathrm{P}_0(y_i < z_{1-\alpha/m}) \\ &= 1 - \Big(1 - \frac{\alpha}{m}\Big)^m \overset{m\to\infty}{\to} 1 - e^{-\alpha} \approx \alpha \end{aligned}$$

For $\alpha = 0.05$, the size is 0.0487 (asymptotically)

Magnitude of the critical value

- We have
$$\mathrm{P}(Z > t) \leq \frac{\phi(t)}{t}$$
- To see this
$$\int_t^\infty \frac{1}{\sqrt{2\pi}} e^{-z^2/2} dz < \frac{1}{t\sqrt{2\pi}} \int_t^\infty z e^{-z^2/2} dz = \frac{1}{t\sqrt{2\pi}} e^{-t^2/2}$$
- It follows that
$$\mathrm{P}(Z > \sqrt{2\log m}) \leq \frac{\phi(\sqrt{2\log m})}{\sqrt{2\log m}} = \frac{1}{2m\sqrt{\pi \log m}} < \frac{\alpha}{m}$$
as soon as $\sqrt{\log m} > \frac{1}{2\sqrt{\pi}\alpha}$
- Therefore $z_{1-\alpha/m} \leq \sqrt{2\log m}$ if $\sqrt{\log m} > \frac{1}{2\sqrt{\pi}\alpha}$

Magnitude of the critical value

- It can be proved that $(1 - 1/t^2)\frac{\phi(t)}{t} < \mathrm{P}(Z > t)$
- Then, for any fixed α and $\epsilon > 0$, the following inequalities hold for all large enough m:

$$\sqrt{(1-\epsilon)2\log(m)} \leq z_{1-\alpha/m} \leq \sqrt{2\log(m)}$$

  Hence, $z_{1-\alpha/m}$ grows like $\sqrt{2\log m}$
- For large m, the maximum test rejects H_0 when

$$T_{\max} \geq \sqrt{2\log m}$$

  and there is (asymptotically) no dependence on α

Needle in a haystack problem

$$H_0 : \mu_i = 0 \text{ for all } i = 1, \ldots, m$$
$$H_1 : \mu_i = c > 0,\ \mu_j = 0 \text{ for } j \neq i$$

- What is the limiting power of the test?

$$\lim_{m\to\infty} \mathrm{P}_1(T_{\max} > z_{1-\alpha/m})$$

- The answer to this question depends on the limiting ratio

$$\lim_{m\to\infty} \frac{c}{\sqrt{2\log m}}$$

where $c = c(m)$ is the value of the single non-zero mean, which is a function of m

Needle in a haystack problem

Two cases:

- Suppose $c > (1+\epsilon)\sqrt{2\log m}$. Then, assuming without loss of generality that $\mu_1 = c$,

$$\mathrm{P}_1(T_{\max} > z_{1-\alpha/m}) \geq \mathrm{P}_1(y_1 > z_{1-\alpha/m}) = \mathrm{P}(Z > z_{1-\alpha/m} - c) \to 1$$

- Suppose $c < (1+\epsilon)\sqrt{2\log m}$. Then

$$\begin{aligned}
\mathrm{P}_1(T_{\max} > z_{1-\alpha/m}) &\leq \mathrm{P}(y_1 > z_{1-\alpha/m}) + \mathrm{P}(\max_{i>1} y_i > z_{1-\alpha/m}) \\
&= \mathrm{P}(Z > z_{1-\frac{\alpha}{m}} - c) + \mathrm{P}(\max_{i>1} y_i > z_{1-\frac{\alpha}{m}}) \\
&\to 0 + (1 - e^{-\alpha}) \approx \alpha
\end{aligned}$$

- Can we do better than this test? No, it is asymptotically equivalent to optimal test given by Neyman-Pearson lemma

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Sum of statistics

$$T_{\mathrm{sum}} = \sum_{i=1}^{m} y_i \sim N(\sum_{i=1}^{m} \mu_i, m)$$

- $Z_{\mathrm{sum}} = \frac{T_{\mathrm{sum}}}{\sqrt{m}} \overset{H_0}{\sim} N(0,1)$
- $Z_{\mathrm{sum}} \overset{H_1}{\sim} N(\theta,1)$ where $\theta = \frac{\sum_{i=1}^{m} \mu_i}{\sqrt{m}}$
- If $\theta \to 0$ when $m \to \infty$, then the test has no power
- By the Neyman-Pearson lemma, T_{sum} is the uniformly most powerful (UMP) test for testing against a dense alternative with constant effect:

  $H_0 : \mu_i = 0$ for all i
  $H_1 : \mu_i = c > 0$ for all i
- Here $\theta = \sqrt{m}c$, but if $c = \frac{1}{m}$ the optimal test has no power

Comparison

The two test are effective in two different regimes:

- **Few strong effects**:
  $m^{1/4}$ of the μ_is are equal to $\sqrt{2\log m}$, the rest 0.
  E.g. when $m = 10^6$, $n^{1/4} \approx 36$ and $\sqrt{2\log m} \approx 5.3$. In this setting $T_{\max}$ has full power, but T_{sum} has no power because

$$\theta = \frac{m^{1/4}\sqrt{2\log m}}{\sqrt{m}} \to 0$$

- **Small, distributed effects**:
  $\sqrt{2m}$ of the μ_is are equal to 3, the rest 0.
  The T_{sum} has (almost) full power, but $T_{\max}$ has no power because when m is large it's very likely that the largest y_i value comes from a null μ_i, not a true signal. An intuitive argument is as follows: among the nulls, the largest y_i has size $\approx \sqrt{2\log m}$ while among the true signals, the largest y_i has size $\approx 3 + \sqrt{2\log\sqrt{2m}}$. If m is large, the former is larger

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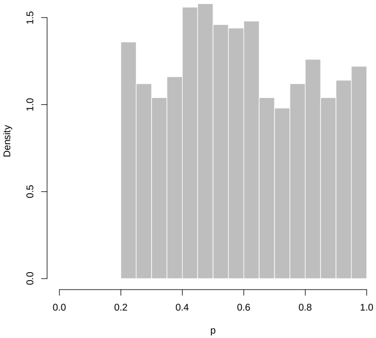
- Suppose that $p_1, \ldots, p_m$ are independent and $p_i \overset{H_0}{\sim} U(0,1)$
- For $m = 1000$ you observe the following histogram of p-values:



- Would you reject the global null hypothesis H_0?
- Note that in this case $H_0 : p_1, \ldots, p_m$ i.i.d. $U(0,1)$

Kolmogorov-Smirnov test

- Consider the empirical CDF $\hat{F}_m(t) = \frac{\sum_{i=1}^m \mathbb{1}\{p_i \leq t\}}{m}$
- Under H_0, each p_i has marginal distribution $U(0,1)$ thus $\mathbb{E}_0(\hat{F}_m(t)) = t$
- Moreover, if we assume that p_is are independent, i.e. $p_1, \dots, p_m$ i.i.d. $U(0,1)$ under H_0, then

$$m\hat{F}_m(t) \sim \mathrm{Binomial}(m, t)$$

- Hence, we measure the distance between what we observe and what we expect and reject if the difference is large, e.g. the Kolmogorov-Smirnov test statistic

$$T_{\mathrm{KS}} = \sup_{t \in [0,1]} |\hat{F}_m(t) - t|$$

Dvoretzky-Kiefer-Wolfowitz inequality

- Given m, let $y_1, \ldots, y_m$ be real-valued i.i.d. r.v. with cdf F and let $\hat{F}_m$ denote the associated ecdf. Then for a a given constant $\epsilon > 0$

$$\mathrm{P}(\|\hat{F}_m - F\|_\infty > \epsilon) \leq 2e^{-2m\epsilon^2}$$

where $\|\hat{F}_m - F\|_\infty = \sup_{t \in [0,1]} |\hat{F}_m(t) - F(t)|$.

- It can be rephrased as follows:

$$\|\hat{F}_m - F\|_\infty \leq \sqrt{\frac{\log \frac{2}{\alpha}}{2m}}$$

with probability $\geq 1 - \alpha$

Higher criticism

- This test statistic is designed to take account for the variance in the Binomial distribution of the statistic T_{KS}

$$T_{\mathrm{HC}} = \sup_{0 \le t \le \alpha_0} \frac{\hat{F}_m(t) - t}{\sqrt{t(1-t)/m}}$$

- It can be equivalently written as follows:

$$T_{\mathrm{HC}} = \max_{0 \le i \le m\alpha_0} T_i, \quad T_i = \sqrt{m} \frac{(i/m) - p_{(i)}}{\sqrt{p_{(i)}(1 - p_{(i)})}}$$

where $p_{(1)} \le \ldots \le p_{(n)}$ are the sorted p-values

Critical value

- T_{HC} can be connected with the maximum of a standardized empirical process. For $m \to \infty$, $b_m T_{\mathrm{HC}} - c_m$ converges weakly to the standard Gumbel distribution, where $b_m = \sqrt{2 \log \log m}$ and $c_m = \frac{1}{2}(\log \log \log(m) - 4\pi)$
- For any fixed α and $m \to \infty$, the $1 - \alpha$ quantile of the null distribution for T_{HC} is

$$t_{1-\alpha} \approx (1 + a)\sqrt{2 \log \log m}$$

  for some $a > 0$, e.g. $a = 1.08$ for $m \approx 10^6$, $\alpha_0 = 1$ and $\alpha = 0.05$ by simulations

Mixture distribution

- We assume that our samples follow a mixture of $N(0,1)$ and $N(\mu,1)$ distributions with μ fixed, resulting in

$$\begin{aligned} H_0 &: \quad y_i \overset{i.i.d}{\sim} N(0,1) \\ H_1 &: \quad y_i \overset{i.i.d}{\sim} \pi_0 N(0,1) + \pi_1 N(\mu,1) \end{aligned}$$

  where $\pi_1 = 1 - \pi_0$
- To carry out asymptotic analysis, we must specify the dependence scheme of $\pi_1 = \pi_1(m)$ and $\mu = \mu(m)$ on m:

$$\begin{aligned} \pi_1 = m^{-\beta} &\qquad \frac{1}{2} < \beta < 1 \\ \mu = \sqrt{2r \log m} &\qquad 0 < r < 1 \end{aligned}$$

- Note that The needle in a haystack problem corresponds to $\beta = 1$ and $r = 1$; the small distributed effects case corresponds to $\beta = 1/2$

Threshold curve

The following threshold curve for r

$$\rho_{\mathrm{HC}}(\beta) = \begin{cases} \beta - \frac{1}{2} & \text{if } \frac{1}{2} < \beta \leq \frac{3}{4} \\ (1 - \sqrt{1-\beta})^2 & \text{if } \frac{3}{4} \leq \beta \leq 1 \end{cases}$$

is such that

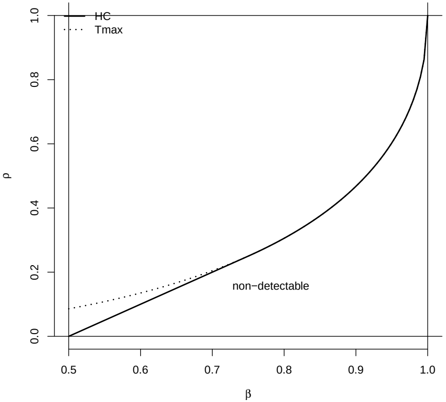
- If $r > \rho_{\mathrm{HC}}(\beta)$ the Neyman-Pearson optimal test achieves

  $$\mathrm{P}_0(\text{Type I Error}) + \mathrm{P}_1(\text{Type II Error}) \to 0$$

  The Higher Criticism is asymptotically equivalent to the optimal test without knowledge of π_1 and/or μ
- If $r < \rho_{\mathrm{HC}}(\beta)$ then for *any* test

  $$\liminf_{m \to \infty} \mathrm{P}_0(\text{Type I Error}) + \mathrm{P}_1(\text{Type II Error}) \geq 1$$

Detectable region



$$\rho_{\mathrm{Tmax}}(\beta) = (1 - \sqrt{1-\beta})^2$$