

Biostat 279 Hw 1

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- 1 Suppose you wish to design a randomized two-arm controlled trial to detect a clinically important difference equal to the standard deviation at the 5% significance level. If the study recruits 30 patients, show that the power is $\phi((n_1 n_2 / 30)^{1/2} - 1.96)$, where ϕ is the cumulative density function of the standard normal and n_1 patients are assigned to one group and n_2 to the other group with $n_1 + n_2 = 30$. Use this result to show
- A if the group sizes are equal, then the power is about 78%.
 - B if one has group has size 20 and the other has 10, then the power is about 73%.
 - C if one group has size 6 and the other has 24, then the power is 59%.

What is the take home message, if any, from the above calculations? Develop the corresponding formula for the power if we wish to recruit n patients (instead of 30) so that $n_1 + n_2 = n$, and use it to show that power is maximized when $n_1 = n_2$.

- 2 Show that the Neyman's optimal allocation scheme can be unethical in a two-arm trial with a binary outcome when the sum of the response probabilities of success for the two treatments exceeds 1.
- 3 Verify that the optimal allocation for a two-arm trial with a binary outcome is as given in the lecture note titled "Some optimal allocation rules" on Week 1 of the class website when odds ratio is used to compare performance of the two treatments.
- 4 Find the best two-point approximate design for estimating the two coefficients in the quadratic model without intercept on the interval $[-1, 1]$.
- A Is the best two-point approximate design for minimizing the sum of the variances of the two estimated parameters the same two-point design you found above?
 - B Calculate the D and A-efficiencies of the first design relative to the second design. Is any one of the two designs you found above A or D-optimal? Why?
- 5 Verify (i) the information matrix shown in Table 4 of Reading Material for the two-parameter logistic model and (ii) the information matrix of the exponential distribution in the Technometrics paper. Both references are posted on Week 3 on the class website.

- 1 Find the D-optimal design for the model $E(y) = a x + b x^2 + c x^3$ on the dose interval $[0, 4]$ and compute the D-efficiencies of the uniform design supported at 3, 5 and 7 points.
- 2 Consider the nonlinear model with mean response given by

$$g(x,a,b) = \frac{a}{a-b} \{ \exp(-bx) - \exp(-ax) \}, \quad b > a \text{ and } x > 0.$$

This model is extremely useful in the modeling of phenomena as diverse as chemical reactions and the movement of drugs through the body (pharmacokinetics). Assume all errors are independent and identically distributed with mean 0 and constant variance.

- A Calculate the information matrix for an observation taken at x .
 - B Find the best two-point design for estimating the two parameters a and b assuming nominal values are $a = 0.2$ and $b = 0.7$. Make clear what you meant by best.
 - C In practice, nominal values may be incorrect. If you had assumed wrongly nominal values are $a = 0.3$ and $b = 0.5$, what is the loss in efficiency of your design relative to the optimal two-point design you found in (B).
 - D Is your best two-point design in (B) best among all designs? Justify.
 - E If you are only interested to estimate b in the above model, describe how you would design your study. Provide justifications.
- 3 Suppose you want to design a Phase 2 design with a binary outcome with 90% power for testing the hypothesis $H_0: p \leq 0.2$ versus $H_a: p \geq 0.45$ at the 0.05 significance level. Here p is the probability of response from a patient given a particular dose of a drug.

Describe two ways how you would design such a study, making clear your statistical rejection rule.

Problem 1:

1 Suppose you wish to design a randomized two-arm controlled trial to detect a clinically important difference equal to the standard deviation at the 5% significance level. If the study recruits 30 patients, show that the power is $\Phi((n_1 n_2 / 30)^{1/2} - 1.96)$, where Φ is the cumulative density function of the standard normal and n_1 patients are assigned to one group and n_2 to the other group with $n_1 + n_2 = 30$. Use this result to show

- A if the group sizes are equal, then the power is about 78%.
- B if one has group has size 20 and the other has 10, then the power is about 73%.
- C if one group has size 6 and the other has 24, then the power is 59%.

What is the take home message, if any, from the above calculations? Develop the corresponding formula for the power if we wish to recruit n patients (instead of 30) so that $n_1 + n_2 = n$, and use it to show that power is maximized when $n_1 = n_2$.

Sol. Power is $\Phi\left(\frac{\sqrt{n_1 n_2}}{30} - Z_{0.025}\right)$.

Pf: We have

$$X_i \sim N(\mu_1, \sigma^2), i=1, \dots, n_1,$$

$$Y_i \sim N(\mu_2, \sigma^2), i=1, \dots, n_2,$$

& σ^2 is known & $H_0: \mu_1 = \mu_2$, $H_1: \mu_1 - \mu_2 = 6$

Then

$$\frac{\bar{X} - \bar{Y} - 6}{\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}} \stackrel{H_1}{\sim} N(0, 1)$$

Let $C = \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} = \sqrt{\frac{n_1 + n_2}{n_1 n_2}} = \sqrt{\frac{30}{n_1 n_2}}$, then

$$1 - \beta = P\left(\frac{\bar{X} - \bar{Y}}{C \sigma} > 1.96 \mid H_1\right)$$

$$= P\left(\frac{\bar{X} - \bar{Y} - 6}{C \sigma} > 1.96 - \frac{6}{C} \mid H_1\right)$$

$$= \Phi\left(\frac{1}{C} - 1.96\right)$$

$$= \Phi\left(\frac{\sqrt{n_1 n_2}}{30} - 1.96\right) \quad \square.$$

(A) If $n_1 = n_2 = 15$, then $1 - \beta = 78\%$.

Pf:

$$1 - \beta = \Phi\left(\frac{\sqrt{15}}{2} - 1.96\right)$$

$$= 78.19\%.$$

(B) $n_1 = 20$ & $n_2 = 10$.

$$\begin{aligned} Pf &= 1 - \beta = \Phi\left(\frac{\sqrt{20}}{3} - 1.96\right) \\ &= 73.30\%. \end{aligned}$$

(C) $n_1 = 6$ & $n_2 = 24$

$$\begin{aligned} Pf &= 1 - \beta = \Phi\left(\frac{\sqrt{24}}{5} - 1.96\right) \\ &= 59.18\%. \end{aligned}$$

Take home message?

Sol. Equal sample size has the maximum power where variances are equal in 2 groups.

Formula?

Sol. $n_2 = 30 - n_1 \Rightarrow$

$$1 - \beta = \Phi\left(\frac{\sqrt{n_1(n_2)}}{30} - 1.96\right)$$

But $\Phi(t)$ is an monotone increasing function & $\frac{n_1(n_2)}{30}$ is indeed maximized when

$$n_1 = 15 \text{ & } n_2 = 15 \quad \square.$$

$$\bullet \sqrt{n_1 n_2} \leq \frac{n_1 + n_2}{2} = \frac{n}{2}.$$

Q2: $n_A = R n_B$

- 2 Show that the Neyman's optimal allocation scheme can be unethical in a two-arm trial with a binary outcome when the sum of the response probabilities of success for the two treatments exceeds 1.

$$R^* = \sqrt{\frac{P_A q_A}{P_B q_B}}, \text{ if } P_A > P_B \text{ &}$$

$$P_A = 0.9, P_B = 0.5 \Rightarrow R^* = 0.6$$

So A has higher probability of success
but lower proportion of allocation.

- $n_A \propto \sqrt{P_A(1-P_A)}$
 $n_B \propto \sqrt{P_B(1-P_B)}$

Q3:

- 3 Verify that the optimal allocation for a two-arm trial with a binary outcome is as given in the lecture note titled "Some optimal allocation rules" on Week 1 of the class website when odds ratio is used to compare performance of the two treatments.

$$\text{Pf: Let } \Theta = \log \frac{\pi_A(1-\pi_B)}{\pi_B(1-\pi_A)}$$

be the log-odds ratio.

$$\text{Then } \hat{\Theta} = \log \frac{P_A(1-P_B)}{P_B(1-P_A)}, P_A = \frac{\# \text{succ}_A}{n_A}, P_B = \frac{\# \text{succ}_B}{n_B}$$

has asymptotic variance (202B)

$$\text{Var}(\hat{\Theta}) \approx \frac{1}{n_A P_A} + \frac{1}{n_A(1-P_A)} + \frac{1}{n_B P_B} + \frac{1}{n_B(1-P_B)}$$

Set it to K & let

$$n_A = \frac{Rn}{1+R}, n_B = \frac{n}{1+R}$$

so that $n = n_A + n_B$ is fixed,
we have

$$K = \frac{1+R}{n_R P_A} + \frac{1+R}{n_R q_A} + \frac{1+R}{n_B P_B} + \frac{1+R}{n_B q_B}$$

$$\Rightarrow n = \frac{1+R}{K} \left[\frac{1}{R P_A} + \frac{1}{R q_A} + \frac{1}{P_B} + \frac{1}{q_B} \right]$$

To minimize the number of Failures:

$$\mathbb{E}(\#\text{of failures}) = n_A q_A + n_B q_B$$

$$= n \left[\frac{q_A R}{1+R} + \frac{q_B}{1+R} \right]$$

Thus,

$$\min_{R>0} \frac{q_A R + q_B}{K} \left[\frac{1}{R P_A} + \frac{1}{R q_A} + \frac{1}{P_B} + \frac{1}{q_B} \right] \quad (\Delta)$$

$$\frac{\partial(\Delta)}{\partial R} = \frac{1}{K} \left[\frac{q_A}{R P_A} + \frac{1}{R} + \frac{q_A}{P_B} + \frac{q_A}{q_B} - \left(\frac{1}{R^2 P_A} + \frac{1}{R^2 q_A} \right) (q_A R + q_B) \right]$$

$$= 0$$

$$\Rightarrow \frac{q_A}{P_B} + \frac{q_A}{q_B} = \frac{q_B}{R^2 P_A} + \frac{q_B}{R^2 q_A}$$

$$\Rightarrow R^* = \sqrt{\frac{P_B}{P_A}} \times \frac{q_B}{q_A}$$

□

Q4:

- 4 Find the best two-point approximate design for estimating the two coefficients in the quadratic model without intercept on the interval [-1, 1].
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Sol. Two-point approx. design.

$$\mathbb{E}Y = \beta_1 x + \beta_2 x^2$$

Let $f(x) = (x, x^2)$, then

$$\xi = \frac{1}{2} S_{-1} + \frac{1}{2} S_1$$

I verify this is D-optimal.

$$M(\xi) = \frac{1}{2} f(-1)f(-1)^T + \frac{1}{2} f(1)f(1)^T$$

$$= \frac{1}{2} \begin{pmatrix} 1 & -1 \\ -1 & 1 \end{pmatrix} + \frac{1}{2} \begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix}$$

$$= \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$$

Equivalence theorem: $p=2$ &

$$f(x)^T M(\xi)^{-1} f(x) - p$$

$$= x^2 + x^4 - 2 = 0 \quad \text{if } x = \pm 1.$$

Thus, $\xi = \begin{pmatrix} 1 & 1 \\ -1 & 1 \end{pmatrix}$ is indeed

D-optimal. Since $\forall x \in [-1, 1]$,

$x^2 \in [0, 1]$ & thus

$$x^2 + x^4 - 2 \leq 0.$$

$$(A): \text{Var} \begin{pmatrix} \hat{\beta}_1 \\ \hat{\beta}_2 \end{pmatrix} = \sigma^2 (X^T X)^{-1} \\ = \sigma^2 \left(\frac{2}{7} W, f(x)f(x)^T \right)^{-1}$$

Call this (Δ) , then $\text{Var}\hat{\beta}_1 + \text{Var}\hat{\beta}_2$ is the criterion for A-optimality. WLOG, $\sigma^2 = 1$.

Again, $\xi = \begin{pmatrix} 1 & 1 \\ -1 & 1 \end{pmatrix}$, then by equivalence thm,

$$f(x)^T M^{-2} f(x) - \text{Tr } M(\xi)^{-1} \\ = x^2 + x^4 - 2 \leq 0 \quad \forall x \in [-1, 1].$$

So they are the same.

(B):

$$D\text{-eff} = \left(\frac{|M(\xi_1)|}{|M(\xi_2)|} \right)^{\frac{1}{2}} = 1$$

$$A\text{-eff} = \left(\frac{\text{Tr } M(\xi_2)}{\text{Tr } M(\xi_1)} \right) = 1$$

Q5:

- 5 Verify (i) the information matrix shown in Table 4 of Reading Material for the two-parameter logistic model and (ii) the information matrix of the exponential distribution in the Technometrics paper. Both references are posted on Week 3 on the class website.

Sol.

(i) logistic model.

$$\text{pdf} = \frac{1}{b(1+e^{-ay/b})^2} e^{-cy/a/b}, \quad \text{mean: } \frac{a}{b}, \quad \text{variance: } b^2\pi^2/3$$

$$\log f(y|a,b) = -\frac{ya}{b} - \log b - 2 \log(1+e^{-\frac{ya}{b}})$$

$$\bullet u = \frac{y-a}{b}, \quad du = \frac{1}{b} dy,$$

$$\bullet f(u|a,b) = \frac{e^{-u}}{(1+e^{-u})^2}$$

log-likelihood is

$$l = -u + 2 \ln(1+e^{-u})$$

$$\Rightarrow \frac{\partial l}{\partial a} = \frac{\partial l}{\partial u} \frac{\partial u}{\partial a} = \left(-1 + \frac{2e^{-u}}{1+e^{-u}}\right) \left(-\frac{1}{b}\right)$$

$$\frac{\partial^2 l}{\partial a^2} = -\frac{2}{b} \frac{\partial}{\partial a} \frac{e^{-u}}{1+e^{-u}} = -\frac{2}{b^2} \frac{e^{-u}}{(1+e^{-u})^2}$$

$$-\mathbb{E}\left(\frac{\partial^2 l}{\partial a^2}\right) = \frac{2}{b^2} \int_{-\infty}^{+\infty} \frac{e^{-u}}{(1+e^{-u})^4} du = \frac{2}{b^2} \frac{1}{6} = \frac{1}{3b^2}.$$

$$\bullet \frac{\partial^2 l}{\partial b \partial a} = \frac{\partial}{\partial b} \left[\left\{ 1 - \frac{2e^{-u}}{1+e^{-u}} \right\} \frac{1}{b} \right]$$

$$-\mathbb{E} \frac{\partial^2 l}{\partial b \partial a} = -\frac{1}{b^2} + \frac{2}{b^2(1+e^{-u})} - \frac{2}{b^2} \times \frac{e^{-u}}{(1+e^{-u})^2}$$

$$= -\frac{1}{b^2} + \frac{2}{b^2} \frac{1}{2} - 0 = 0.$$

$$\bullet \frac{\partial^2 l}{\partial b^2} = \frac{y^2}{b^4} \left(\frac{2e^{-u}}{(1+e^{-u})^2} \right) - \frac{2y}{b^3} \left(1 + \frac{2e^{-u}}{1+e^{-u}} \right)$$

$$-\mathbb{E}\left(\frac{\partial^2 l}{\partial b^2}\right) = 3 + \frac{3}{b}$$

□.

(ii) exp dist.

See next page

Biostat 279 HW1

Q5 part (ii)

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1 Verify the information matrix of the exponential distribution in the Technometrics paper

Let $S \sim \mathcal{E}(\lambda)$ and $\lambda^{-1} = \frac{A}{(\phi_c - \phi)^\gamma}$ so that λ is a function of $\theta = (A, \phi, \gamma)$. Define

$$x = \phi_c - \phi$$

$$\eta = -\log \lambda = \log A - \gamma \log x$$

Then according to Atkinson's paper, I have

$$\nu(\eta) = \text{Var}\left(\frac{\partial}{\partial \eta} \log p(s|\eta)\right) = 1 \quad (1)$$

$$F(S, \lambda) = \frac{\partial \eta}{\partial \theta} = \left(\frac{1}{A}, \frac{\gamma}{x}, -\log x\right)^T \quad (2)$$

To prove (1), note that by Chain rule,

$$\frac{\partial}{\partial \eta} \log p(s|\eta) = \frac{\partial \lambda}{\partial \eta} \frac{\partial \log p(s|\lambda)}{\partial \lambda}$$

So that

$$\nu(\eta) = \frac{\partial^2 \lambda}{\partial \eta^2} \text{Var}\left(\frac{\partial \log p(s|\lambda)}{\partial \lambda}\right)$$

By Wikipedia, the information matrix for λ in the exponential distribution is $\frac{1}{\lambda^2}$ and $\frac{\partial^2 \lambda}{\partial \eta^2} = e^{-2\eta} = \lambda^2$. Thus,

$$\nu(\eta) = \lambda^2 \times \frac{1}{\lambda^2} = 1$$

To prove (2), take derivative w.r.t. to A, ϕ and γ in the link function $\eta = \log A - \gamma \log x$.

Finally, by lemma 1 in the Atkinson's paper, I have

$$\begin{aligned} \mathcal{I}(\theta) &= F(S, \lambda) \nu(\eta) F(S, \lambda)^T \\ &= \begin{pmatrix} \frac{1}{A^2} & \frac{\gamma}{Ax} & -\frac{\log x}{A} \\ \frac{\gamma}{\gamma^2} & \frac{\gamma^2}{x^2} & -\frac{\gamma \log x}{x} \\ -\frac{\log x}{A} & -\frac{\gamma \log x}{x} & \log^2 x \end{pmatrix} \end{aligned} \quad (3)$$