Bayesian Sample Size Determination Methods for Hypotheses Testing

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Outline

- **Sample size determination (Part I)**
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  - Bayesian Average Errors
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- **Bayesian Non-inferiority tests (Part II)**
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Sample Size Determination (Part I)

- Sample size determination is critical in designing medical studies
- Failure to consider sample size calculations prior to a study can have severe consequences:
  - Studies may lack power to detect clinically important effects
  - An unnecessary number of subjects may be enrolled
- E.g., the study GUSTO III with over 15,000 patients has been found under-powered to assess non-inferiority
- There are a variety of approaches to sample size determination:
  - Adcock (1997): provides an comprehensive review of various approaches
  - Inoue, Berry and Parmigiani (2005): a general framework that connects the classical and Bayesian perspectives

A safety study: Rosuvastatin therapy

- Avis et al.(2010) reported a clinical trial to determine the efficacy of *rosuvastatin therapy* for lowering cholesterol in children with familial hypercholesterolemia
- The treatment with a 20mg dose of rosuvastatin was found effective in lowering cholesterol (against placebo)
- However, the study was not powered on the secondary safety endpoints (e.g., adverse effects of 20mg of rosuvastatin)
- Suppose we want to conduct follow-up studies to assess the safety of rosuvastatin in children
- Avis et al. (2010) reported that 54% and 55% of children experienced adverse events in the placebo and rosuvastatin group
- *Can we use the results of this previous study (as prior knowledge) to determine sample sizes?*

- Consider the problem of comparing event rates of two groups based on dichotomous data
- θ_0: true (unknown) event rate of control group
  θ_1: true (unknown) event rate of experimental group
- The goal is to compare the hypotheses:
$$H_0 : \theta_0 = \theta_1 \text{ vs. } H_1 : \theta_0 \neq \theta_1$$
- Qn.: *How many subjects should we sample from each group to make a decision?*
- Often the target is to control two errors:
  - *Type I error rate* below α (e.g., 0.05)
  - *Type II error rate* below β (e.g., 0.20)
    or equivalently *the power* above $1 - \beta$ (e.g., 0.80)
- For simplicity, assume $n_1 = n_2 = n$ subjects would be sampled

- Classical (frequentist) solution:
$$n \geq \frac{\left(Z_\alpha \sqrt{2\bar{\theta}(1-\bar{\theta})} + Z_\beta \sqrt{\theta_0 (1-\theta_0) + \theta_1 (1-\theta_1)} \right)^2}{(\theta_1 - \theta_0)^2} \quad (1)$$
  where $\bar{\theta} = (\theta_0 + \theta_1)/2$ and Z_α denotes the $1-\alpha$ percentile of a standard normal distribution (e.g., $Z_{0.05} = 1.645$)
- Some obvious but critical issues:
  - n depends on *posited values for the parameters of interest* !!
  - What happens to above solution in (1) if indeed H_0 were true?
  - *No uncertainty about the posited values are accommodated*
  - Pivot quantities not guaranteed to exist (Adcock, 1997)
  - Normal approximations may be questionable (M'Lan, 2008)
  - *Wouldn't large sample based approximations lead to large sample?*

Limitations of Classical Methods

- Calculation of a Type-II error rate often requires the user to posit a value for the parameter under the alternative
- Positing suitable values under a given hypothesis becomes more difficult when the null hypothesis is composite
- Sample size calculations under the classical framework are often based on a pivot quantity
- However, the existence of a pivot quantity is not guaranteed, even in common settings
- Nuisance parameters may be involved in a composite hypothesis
- Elimination via conditioning statistic or estimate of nuisance parameters can rarely be done in practice

Bayesian Approaches

- Consider the general set-up of a Bayesian model:
$$X|\theta \sim f(x|\theta) \text{ and } \theta \sim \pi(\theta) \text{ where } \theta \in \Theta \text{ and } x \in \mathcal{X}$$
- $f(x|\theta)$: joint density of the vector of observations X given θ
- $\pi(\theta)$: prior density of the vector of parameters θ
- Our goal is to compare: $H_0 : \theta \in \Theta_0$ vs. $H_1 : \theta \in \Theta_1$ where $\Theta_0 \cap \Theta_1 = \emptyset$ and $\Theta_0 \cup \Theta_1 \subseteq \Theta$
- Example: if $X_j|\theta_j \sim Bin(n_j, \theta_j)$ for $j = 0, 1$, we have $X = (X_1, X_2)$ and $\theta = (\theta_0, \theta_1) \in \Theta = [0, 1]^2 \equiv [0, 1] \times [0, 1]$
- $H_0 : \theta_0 = \theta_1 \Rightarrow \Theta_0 = \{\theta_0 = \theta_1 : \theta \in [0, 1]^2\}$ and
  $H_1 : \theta_0 \neq \theta_1 \Rightarrow \Theta_1 = \{\theta_0 \neq \theta_1 : \theta \in [0, 1]^2\}$

- We assume: $\Pr_\pi[\theta \in \Theta_j] = \int_{\Theta_j} \pi(\theta)\, d\theta > 0$ for $j = 0, 1$
- In other words, *apriori we shouldn't rule out the possibility of any of the hypotheses*
- Otherwise, no amount of data can test the validity of a hypothesis if a positive probability is not assigned to that hypothesis
- Notice that if we use the usual conjugate prior $\theta_j \sim Beta(a_j, b_j)$ for $j = 0, 1$, the condition $\Pr[\theta \in \Theta_0] = \Pr[\theta_1 = \theta_0] > 0$ is violated!
- Instead we could use the following (conjugate) prior:

$$\pi(\theta) = u\mathbb{I}(\theta_0 = \theta_1 = \eta)\, p_{(a_0,b_0)}(\eta) + (1-u)\mathbb{I}(\theta_0 \neq \theta_1)\, p_{(a_1,b_1)}(\theta_0) p_{(a_2,b_2)}(\theta_1)$$

  where $u = Pr(\theta_1 = \theta_2)$ and $p_{(a,b)}(\theta)$ denotes a Beta(a, b) density
- In above, we can use any other continuous distribution replacing Beta(a, b)
- However, if we are comparing $H_0 : \theta_0 \leq \theta_1$ vs. $H_1 : \theta_0 > \theta_1$, then we can use the usual conjugate prior distributions

- Thus prior distributions should be chosen carefully based on the hypotheses being tested (making sure hypotheses are not ruled out *apriori*)
- In general, one may choose prior distributions satisfying the following condition: $\Pr[\theta \in \Theta_0] \approx \Pr[\theta \in \Theta_1] \approx 0.5$
- In the previous example choosing $u = 0.5$ guarantees the above requirement $\Pr[\theta \in \Theta_0] = \Pr[\theta \in \Theta_1] = 0.5$
- In other words, *apriori* we are not be overly biased in favor of one of the hypotheses (being tested)
- Notice that relatively non-informative priors can be used that also simultaneously satisfy above prior unbiasedness requirement
- E.g., in the previous example of testing $H_0 : \theta_0 = \theta_1$, we can choose to use Beta$(0.5, 0.5)$ (Jeffrey's prior) or the flat Beta$(1, 1)$ prior by choosing $a_0 = b_0 = a_1 = b_1 = a_2 = b_2 = 0.5$ or $= 1$

Bayesian Average Errors for Hypotheses Tests

- Within a frequentist framework, hypotheses are tested by carefully controlling the familiar *Type I & II* errors
- Regulatory purposes and various scientific considerations often necessitates the control of such error probabilities
- Bayesian sample size determination methods are often criticized as not being able to control the error probabilities for testing hypotheses
- This aspect has remained a stumbling block against the automatic adoption of Bayesian methods in clinical trials
- So, *can we built Bayesian methods that allow controlling such error probabilities?*
- More fundamentally, *how do we define similar error probabilities when parameters are random (with assigned prior distributions)?*

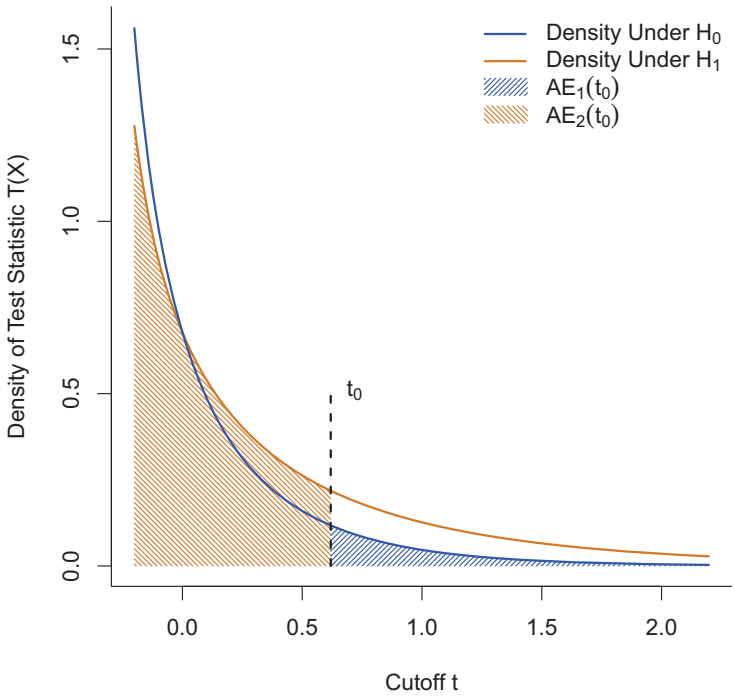
- $T(X)$: a "test statistic" measuring the evidence favoring the alternative hypothesis
- Decision rule: Reject the null hypothesis (in favor of the alternative) if $T(X) > t$ for some cut-off value t
- *How would we choose the cut-off value t?*
- Consider **Bayesian Average Error (AE) rates**:
  $AE_1(t) = \Pr[T(X) > t|\theta \in \Theta_0]$ and $AE_2(t) = \Pr[T(X) \leq t|\theta \in \Theta_1]$
- Above error rates are to be distinguished from the classical errors
- The conditional probability $\Pr[T(X) > t|\theta \in \Theta_j]$ is well defined only when $\Pr[\theta \in \Theta_j] > 0$ for $j = 0, 1$
- The quantity $(1 - AE_2(t))$ may be considered as the average power of the test
- Notice that $AE_j(t)$ does not require the user to posit a value of parameters under both (null and alternative) hypotheses

- The calculation of $AE_j(t)$ is straightforward even when there are nuisance parameters in the composite hypotheses
- Given a prior $\theta \sim \pi(\theta)$ and sampling model $X|\theta \sim f(x|\theta)$, we can compute Bayesian average Type I error probability:

$$\begin{aligned} AE_1(t) &= \Pr[T(X) > t | \theta \in \Theta_0] = \frac{\Pr[T(X) > t, \theta \in \Theta_0]}{\Pr[\theta \in \Theta_0]} \\ &= \frac{\int_{T(x)>t} \int_{\Theta_0} f(x|\theta)\pi(\theta)\, d\theta\, dx}{\int_{\Theta_0} \pi(\theta)\, d\theta} = \int_{T(x)>t} m_0(x)\, dx \end{aligned}$$

  where $m_0(x) = \frac{\int_{\Theta_0} f(x|\theta)\pi(\theta)\, d\theta}{\int_{\Theta_0} \pi(\theta)\, d\theta}$ denotes the marginal distribution of the data under the null hypothesis
- Thus, *we no longer need to obtain a pivot quantity or conditioning statistic to eliminate nuisance parameters*
- However, we do need to compute above (possibly high dimensional) integrals

- Thus, in practice we will often need to employ numerical integration methods (e.g., MCMC methods) to compute both types of Bayesian Average Errors
- Moreover, such computations need to be done in an efficient manner so that we can compute $AE_j(t)$ for any given $t \in \mathbb{R}$
- Notice that $AE_1(t) \leq \sup_{\theta \in \Theta_0} \Pr_\theta[T(X) > t]$ for any $t \in \mathbb{R}$
- In above, the bound is precisely the frequentist level of significance that is controlled to be below a prescribed value (e.g. ≤ 0.05)
- Note that $AE_1(t) = \Pr_{m_0}[T(X) > t]$ is a non-increasing function in t while $AE_2(t) = \Pr_{m_1}[T(X) \leq t]$ is a non-decreasing function
- Thus, as the cut-off t is altered, there is a trade-off between these two Bayesian average error rates
- Hence, we can find a cutoff t that bounds either AE_1 or AE_2 or a weighted average of these Bayesian average errors



- A reasonable approach is to choose a cutoff t that allows for both error rates to be controlled simultaneously
- Hence, consider a *Total Weighted Error (TWE)* criterion:

$$TWE(t, w) = wAE_1(t) + (1 - w)AE_2(t)$$

  where $w \in [0, 1]$ is specified *a priori*
- The weight w can be used to place more emphasis on controlling one type of error over the other
- Given a value of $w \in [0, 1]$, the optimal cutoff $t_0(w)$ is defined as:

$$t_0(w) = \arg\min_t TWE(t, w)$$

- Thus the decision rule becomes: Reject H_0 if $T(X) > t_0(w)$
- *How do we compute $t_0(w)$? How do we find the "optimal" $T(X)$?*

Bayes Factor as Test Statistic

- Consider the *Bayes Factor* in favor of the alternative H_1:

$$BF(X) = \left(\frac{\Pr(\theta \in \Theta_1|X)}{\Pr(\theta \in \Theta_0|X)}\right) / \left(\frac{\Pr(\theta \in \Theta_1)}{\Pr(\theta \in \Theta_0)}\right)$$

- Test statistic: $T(X) = \log BF(X)$
- It is well-known that $T(x) = \log m_1(x) - \log m_0(x)$ where $m_j(x)$ denotes the marginal density under hypothesis H_j for $j = 0, 1$
- Recall that

$$m_j(x) = \frac{\int_{\Theta_j} f(x|\theta)\pi(\theta)\, d\theta}{\int_{\Theta_j} \pi(\theta)\, d\theta} \quad \text{for} \quad j = 0, 1$$

- Thus $T(X) > 0$ would favor H_1. Is 0 a good cutoff value?
  Why should we use Bayes Factor (BF) as a test statistics?

It turns out that BF is indeed optimal among all test functions in the following sense:

Theorem 1. *(Reyes and Ghosh, 2011) Consider testing the hypothesis as described previously. Let BF(X) denote the Bayes factor and let*

$$\varphi(X) : \mathcal{X} \to [0, 1]$$

represent a randomized test for the hypothesis. Then, for a given value of $w \in (0, 1)$, $\hat{\varphi}(X)$ minimizes $TWE(t, w)$ where

$$\hat{\varphi}(X) = \mathbb{I}\left(BF(X) > \frac{w}{1-w}\right).$$

Implications:

- $T(X) = \log(BF(X))$ **is optimal among all test functions**
- $t_0(w) = \log \frac{w}{1-w}$ **(universally!)**

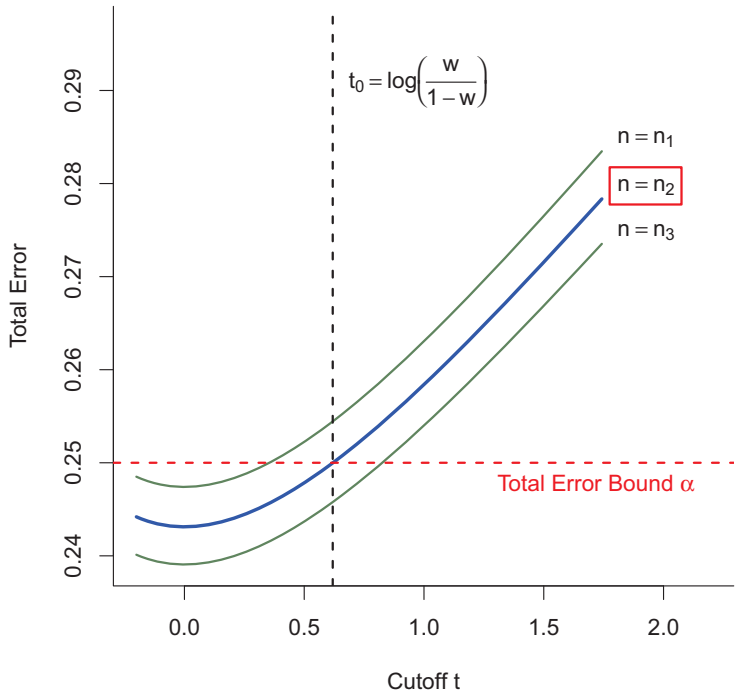
Bayesian Sample Size Determination

- The goal of any test is to control the two errors AE_1 and AE_2
- Given $\alpha, \beta \in (0,1)$, we usually take a two-step approach:
  - Bound $AE_1 \leq \alpha$ by finding a cutoff value t
  - Obtain n such that $AE_2 \leq \beta$
- Alternatively, we can also use a single step approach:

  Given a $w \in (0,1)$*, obtain the minimum* n *such that*

$$TE(t_0(w)) \leq \alpha + \beta$$

  where $TE(t) = AE_1(t) + AE_2(t)$ *denotes the Total Error (TE)*
- Notice that $TE(t) = 2\, TWE(t, 0.5)$
- Hence, $w = 0.5$ provides the smallest sample size



- For a fixed total error bound (e.g., $TE \leq \alpha + \beta$), the weight that will produce the smallest sample size is $w = 0.5$
- If $\Pr(\theta \in \Theta_0) \approx \Pr(\theta \in \Theta_1)$ then $w = 0.5$ is equivalent to rejecting the null H_0 when $\Pr(\theta \in \Theta_0|X) < \Pr(\theta \in \Theta_1|X)$
- Choosing $w = 0.5$ seems a good rule of thumb if there is no strongly preferred bound on AE_1 or AE_2
- What if the goal is to control AE_1 below α?

Theorem 2. *(Osman and Ghosh, 2011) Consider testing the hypothesis as described previously. Let $T(X) = \log BF(X)$ denote the test statistic with cutoff $t_0(w) = \log(w/(1-w))$ for a given $w \in (0,1)$. There exists $w_0 \in (0,1)$ such that for any $w > w_0$, we have,*

$$AE_1(t_0(w)) \leq TWE(t_0(w), w) \leq 1 - w$$

Implication: If we want $AE_1 \leq \alpha$ then choose $w = 1 - \alpha$

Numerical Illustrations

Consider again comparing two binomial proportions:

$X_j|\theta_j \sim Bin(n_j, \theta_j)$ for $j = 0, 1$

Want to compare: $H_0 : \theta_0 = \theta_1$ vs. $H_1 : \theta_0 \neq \theta_1$

Prior distributions:

- Under H_0: Assume $\theta_0 = \theta_1 = \eta \sim Beta(a_0, b_0)$ w.p. u
- Under H_1: Assume $\theta_j \sim Beta(a_{j+1}, b_{j+1})$ for $j = 0, 1$ w.p. $1 - u$

In other words, if $\theta = (\theta_0, \theta_1)$, we have

$$\pi(\theta) = u\mathbb{I}(\theta_0 = \theta_1 = \eta)\, p_{(a_0,b_0)}(\eta) + (1-u)\mathbb{I}(\theta_0 \neq \theta_1)\, p_{(a_1,b_1)}(\theta_0) p_{(a_2,b_2)}(\theta_1)$$

We set $u = 0.5$ and $TE \leq 0.25$ for all calculations

Prior Parameters						Results			
a_0	b_0	a_1	b_1	a_2	b_2	w	n	AE_1	AE_2
1	1	1	1	1	1	0.99	285	0.0001	0.2498
1	1	1	1	1	1	0.95	202	0.0011	0.2482
1	1	1	1	1	1	0.90	172	0.0028	0.2467
1	1	1	1	1	1	0.50	111	0.0429	0.2065
1	1	1	1	1	1	0.10	827	0.2018	0.0479

Recall that $a_0 = b_0 = 1$ correspond to $U(0,1)$ prior on η under H_0 and $a_1 = b_1 = a_2 = b_2 = 1$ correspond $U(0,1)$ priors on θ_0 and θ_1 under H_1

Notice that for this example $w = 0.5$ not only provides smallest sample size of 111 but it also ensures $AE_1 \approx 0.05$ and $AE_2 \approx 0.2$ as desired by regulatory agencies

Prior Parameters						Results			
a_0	b_0	a_1	b_1	a_2	b_2	w	n	AE_1	AE_2
1	1	$15/16$	$5/16$	$5/16$	$15/16$	0.99	52	0.0001	0.2485
1	1	$15/16$	$5/16$	$5/16$	$15/16$	0.95	37	0.0012	0.2487
1	1	$15/16$	$5/16$	$5/16$	$15/16$	0.90	32	0.0028	0.2452
1	1	$15/16$	$5/16$	$5/16$	$15/16$	0.50	20	0.0554	0.1916
1	1	$15/16$	$5/16$	$5/16$	$15/16$	0.10	136	0.2019	0.0472

Recall that $a_0 = b_0 = 1$ correspond to $U(0,1)$ prior on η under H_0 and $a_1 = b_2 = 15/16$ and $b_1 = a_2 = 5/16$ correspond to highly skewed priors on θ_0 and θ_1 under H_1

Here again for this case $w = 0.5$ not only provides smallest sample size of 20 but it also ensures $AE_1 \approx 0.05$ and $AE_2 \approx 0.2$

In fact, we can choose w to ensure $AE_1 \leq 0.05$ as closely as possible and $AE_2 \leq 0.2$ as closely as possible

A Comparison with classical methods:

	$d = \theta_1 - \theta_0$					
	0	0.1	0.2	0.3	0.4	0.5
n_c	∞	392	97	43	24	15
$n_{w=0.9}$	172	159	127	87	54	32
$n_{w=0.5}$	111	103	82	56	35	20
$n_{w=0.1}$	827	762	603	404	240	136

Recall that the classical sample size formula:

$$n_c = \frac{\left(Z_\alpha \sqrt{2\bar{\theta}(1-\bar{\theta})} + Z_\beta \sqrt{\theta_0 (1-\theta_0) + \theta_1 (1-\theta_1)} \right)^2}{(\theta_1 - \theta_0)^2}$$

We have used $\alpha = 0.05$ and $\beta = 0.20$

Back to Rosuvastatin Therapy

- Using the Avis et al. (2010) study, we chooses the following prior parameters
  (1) Under H_0: $\eta \sim$ Beta with mean 0.545 & variance 0.125
  (2) Under H_1: $\theta_0(\theta_1) \sim$ Beta with mean 0.54 (0.55) with a variance of 0.125 for the placebo (rosuvastatin) group
- We set $u = 0.5$ and $TWE \leq \alpha + \beta = 0.15$
- Using $w = 0.5$, required sample size is $\mathbf{n = 243}$ subjects for each treatment arm, yielding an $AE_1 = 0.021$ and $AE_2 = 0.129$
- Reyes and Ghosh (2011) presents results based on a second study to determine if the treatment impairs renal function
- The change in Glomerular Filtration Rate (GFR) from baseline through 12 weeks of treatment is considered as the response

R package: BAEssd

Download the R package from CRAN site:

https://cran.r-project.org/web/packages/BAEssd/

```
#install the package
> install.packages('BAEssd')
#load the package after installation
> library(BAEssd)
#generate suite of function by specifying prior
> fn=binom2.2sided(prob=0.5,a0=1,b0=1,a1=1,b1=1,a2=1,b2=1)
#attach the suite
> attach(fn)
#compure log(BF) for a given data
> logbf(n=30,x=c(12,22))
[1] 2.170515
```



```
#compute the log marginal densities
> logm(n=30,x=c(12,22))
$logm0
[1] -9.03849
$logm1
[1] -6.867974
$logm
[1] -7.453058

> ssd.binom(alpha=0.25,w=0.5,logm=logm,two.sample=TRUE)

Bayesian Average Error Sample Size Determination
Call: ssd.binom(alpha = 0.25, w = 0.5, logm = logm, two.sample = TRUE)
Sample Size:  111
Total Average Error:  0.2494102
Acceptable sample size determined!

> ssd.binom(alpha=0.25,w=0.95,logm=logm,two.sample=TRUE)
```

```
Bayesian Average Error Sample Size Determination
Call: ssd.binom(alpha = 0.25, w = 0.95, logm = logm, two.sample = TRUE)
Sample Size:  202
Total Average Error:  0.2493688
Acceptable sample size determined!

> ssd.binom(alpha=0.2,w=0.5,logm=logm,two.sample=TRUE)

Bayesian Average Error Sample Size Determination
Call: ssd.binom(alpha = 0.2, w = 0.5, logm = logm, two.sample = TRUE)
Sample Size:  192
Total Average Error:  0.1998955
Acceptable sample size determined!
```


END OF PART I

THANKS!

Dhanyavaad धन्यवाद

Non-inferiority Tests (Part II)

- Selecting an appropriate control group is a very important step in many medical studies
- A placebo group is the most ideal candidate for the control
- However, use of placebo may be infeasible due to ethical concerns (*should we assign patients with life-threatening disease to placebo?*)
- Sometimes a placebo control is just impossible due to the nature of some treatment (e.g., *device implant or surgery*)
- Hence, an active control is used to compare against the experimental treatment
- Generally, the best available treatment is selected as the active control (e.g., to avoid "biocreep")

- Establishing superiority of a new treatment over the active control usually turns out to be a difficult task
- Instead, it may be acceptable to show the experimental treatment is not inferior to the standard treatment by some small margin
- There are two crucial issues:
  - *What dissimilarity metric should we use to compare the treatment effects?*
  - *How would we choose the ("small") margin given a dissimilarity metric?*
- In this talk we *do not* address the above issues!
- But check out the previous KOL lecture (03/16/2018) by another 'Ghosh'!!
- We provide methodologies for a general dissimilarity metric and a given margin
- Finally, we discuss only the case of comparing two independent populations with binary end points

- Consider a two-arm study:

	Active control	Experimental
#Events	X_1	X_2
#Subjects	n_1	n_2

- Assume that $X_j \sim Bin(n_j, \theta_j)$ for $j = 1, 2$
- Non-inferiority tests involve comparing hypotheses:

$$H_0 : \theta_2 - \theta_1 \leq -\delta \quad \text{vs.} \quad H_1 : \theta_2 - \theta_1 > -\delta$$
$$H_0 : \theta_2 \leq \rho\theta_1 \quad \text{vs.} \quad H_1 : \theta_2 > \rho\theta_1$$
$$H_0 : \frac{\theta_2}{1-\theta_2} \leq \eta\frac{\theta_1}{1-\theta_1} \quad \text{vs.} \quad H_1 : \frac{\theta_2}{1-\theta_2} > \eta\frac{\theta_1}{1-\theta_1}$$

- All three dissimilarity metrics (i.e., absolute difference, relative risk and odds ratio) have both advantages and disadvantages

- In above, the margins (i.e., δ, ρ and η) are chosen suitably
- All of the above three hypotheses can be expressed as:

$$H_0 : \theta_2 \leq g(\theta_1, \rho) \quad \text{vs.} \quad H_1 : \theta_2 > g(\theta_1, \rho)$$

  where $g(\theta_1, \rho)$ is continuous (often increasing) function of θ_1 and ρ is pre-determined margin
- Following previous notations, let $\theta = (\theta_1, \theta_2) \in \Theta = [0, 1]^2$
- The hypotheses can equivalently be expressed as

$$H_0 : \theta \in \Theta_0 = \{\theta \in \Theta : \theta_2 \leq g(\theta_1, \rho)\}$$
vs.
$$H_1 : \theta \in \Theta_1 = \{\theta \in \Theta : \theta_2 > g(\theta_1, \rho)\}$$

- What prior distribution(s) should we be using for this study?
- *Can we find a flexible prior that are not biased toward H_j's?*

In other words, we would like $\Pr[\theta \in \Theta_0] \approx \Pr[\theta \in \Theta_1]$

- Both parametric and semi-parametric methods are available
- Parametric (conjugate) priors (Osman and Ghosh, 2010):
  Assume that $\theta_j \sim Beta(a(\rho), a(\rho))$ for $j = 1, 2$ where $a(\rho)$ is determined as follows:
$$\tilde{a}(\rho) = \arg \min_{a \in [0,1]} |\Pr[\theta_2 \leq g(\theta_1, \rho) | a(\rho) = a] - 0.5|$$
- The probability $\Pr[\theta_2 \leq g(\theta_1, \rho)]$ can be computed efficiently using (very fast) numerical integrations
- Once the prior $Beta(\tilde{a}, \tilde{a})$ is determined for a given value of ρ, the posterior becomes
$$\begin{aligned} \theta_1 | x_1 &\sim Beta(\tilde{a} + x_1, \tilde{a} + n_1 - x_1) \text{ and} \\ \theta_2 | x_2 &\sim Beta(\tilde{a} + x_2, \tilde{a} + n_2 - x_2). \end{aligned} \quad (2)$$

- Hence, Bayes factor based tests can be easily performed for any dissimilarity metric ($g(\cdot, \rho)$) and associated margin (ρ)
- Sample size determination can thus be performed easily as well
- Notice that for any ρ, the prior parameter $\tilde{a}(\rho) \leq 1$ and hence the priors are not informative
- Also, for any ρ, by the construction of $\tilde{a}(\rho)$ we have $\Pr[\theta \in \Theta_0] \approx \Pr[\theta \in \Theta_1]$
- Notice that no Monte Carlo (MC) simulation based methods are needed for this general approach
- How robust is this method against the prior specifications?
- *Can we relax the assumption of Beta distributions?*
- But...not necessarily at the cost of computing inefficiencies
- Recall that sample size determination could be computationally intensive if the inference is based on MC methods

Semi-parametric Priors

- Assume that $\theta_j \sim \pi_j(\cdot)$ for $j = 1, 2$ where $\pi_j(\cdot)$ is a continuous density on $[0, 1]$
- Bernstein-Weierstrass Approximation:

$$\sum_{i=0}^{m} \pi\left(\frac{i}{m}\right)\binom{m}{i}\theta^i(1-\theta)^{m-i} \to \pi(\theta) \quad \text{uniformly as } m \to \infty$$

  if $\pi(\cdot)$ is a continuous function on $[0, 1]$
- Thus, a mixture of Beta priors of the form $Beta(i + 1, m - i + 1)$ for $i = 0, 1, \ldots, m$ can approximate any arbitrary continuous prior density on $[0, 1]$
- How would we select the mixing weights and number of components?

- Next we assume that for a suitably chosen m,

$$\theta_1 \sim \sum_{i=0}^{m} w_{1i} f_b(\theta_1; i + 1, m - i + 1)$$

$$\theta_2 \sim \sum_{i=0}^{m} w_{2i} f_b(\theta_2; i + 1, m - i + 1)$$

  where $f_b(\theta; a, b)$ denotes the density of $Beta(a, b)$ distribution
- The weights must satisfy the constraint:

$$w_{ji} \geq 0 \quad \text{and} \quad \sum_{i=0}^{m} w_{ji} = 1 \quad \text{for} \quad j = 1, 2$$

- Once the weights are determined, the above mixture is also a conjugate prior for this problem
- Hence it is enough to obtain methodologies for computing the prior probabilities

- It can be shown that the probability of null can be expressed as:

$$\Pr[\theta \in \Theta_0] = \Pr[\theta_2 \leq g(\theta_1, \rho)] = \boldsymbol{w}_1^T \boldsymbol{A} \boldsymbol{w}_2$$

  where $\boldsymbol{w}_1^T = (w_{10}, w_{11}, \ldots, w_{1m})$ and $\boldsymbol{w}_2^T = (w_{20}, w_{21}, \ldots, w_{2m})$

- The $(m+1) \times (m+1)$ matrix $\boldsymbol{A}$ can be computed using (very efficient) numerical integrations (Osman and Ghosh, 2011)
- For simplicity we can assume $\boldsymbol{w}_1 = \boldsymbol{w}_2 = \boldsymbol{w}$ and obtain the $\boldsymbol{w}$ solving the following optimization problem:

$$\hat{\boldsymbol{w}} = \arg\min |\boldsymbol{w}^T \boldsymbol{A} \boldsymbol{w} - 0.5| \text{ subj to } \boldsymbol{w} \geq \boldsymbol{0}, \boldsymbol{w}^T \boldsymbol{1} = 1$$

- We also use an additional constraint: $w_i = w_{m-i}$ for $i = 0, 1, \ldots$
- Thus, $\hat{\boldsymbol{w}}$ can be obtained by quadratic programming
- The resulting semi-parametric prior then satisfies: $\Pr[\theta \in \Theta_0] \approx \Pr[\theta \in \Theta_1]$ (for any arbitrary m, $g(\cdot, \rho)$ and ρ!)

- The posterior density can be computed analytically (as mixture of Beta's is still conjugate)
- Hence, the posterior probability of the null hypothesis is:

$$Pr[(\theta_1, \theta_2) \in \Theta_0 | X_1 = x_1, X_2 = x_2] = \boldsymbol{w_1}^{*T} H \boldsymbol{w_2}^*,$$

  where $\boldsymbol{w}_j^* = (w_{j0}^*, w_{j1}^*, \ldots, w_{jm}^*)^T$ and $w_{ji}^* \propto w_{ji} \frac{m+1}{m+n_j+1} \frac{\binom{n_j}{x_j}\binom{m}{i}}{\binom{m+n}{x_j+i}}$

- The elements of $H = H(x_1, x_2)$ is given by

$$h_{pq}(\rho) = \int_0^1 [F_\beta(g(\theta_1, \rho); x_2 + q, m + n_2 - x_2 - q + 2)] f_\beta(\theta_1; x_1 + p, m + n_1 - x_1 - p + 2) d\theta_1$$

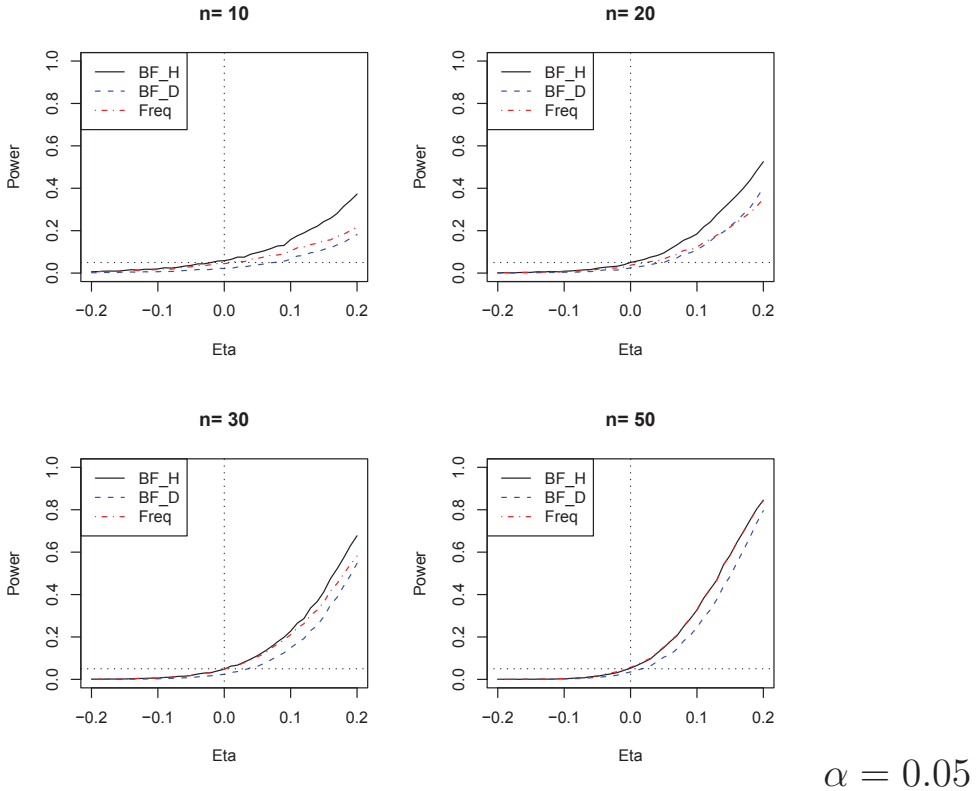
- And, finally the BF can be computed analytically as well!

$$BF(x_1, x_2) = \frac{\boldsymbol{w_1}^{*T} H \boldsymbol{w_2}^*}{1 - \boldsymbol{w_1}^{*T} H \boldsymbol{w_2}^*} \cdot \frac{1 - \boldsymbol{w_1}^T A \boldsymbol{w_2}}{\boldsymbol{w_1}^T A \boldsymbol{w_2}} \approx \frac{\boldsymbol{w_1}^{*T} H \boldsymbol{w_2}^*}{1 - \boldsymbol{w_1}^{*T} H \boldsymbol{w_2}^*}$$

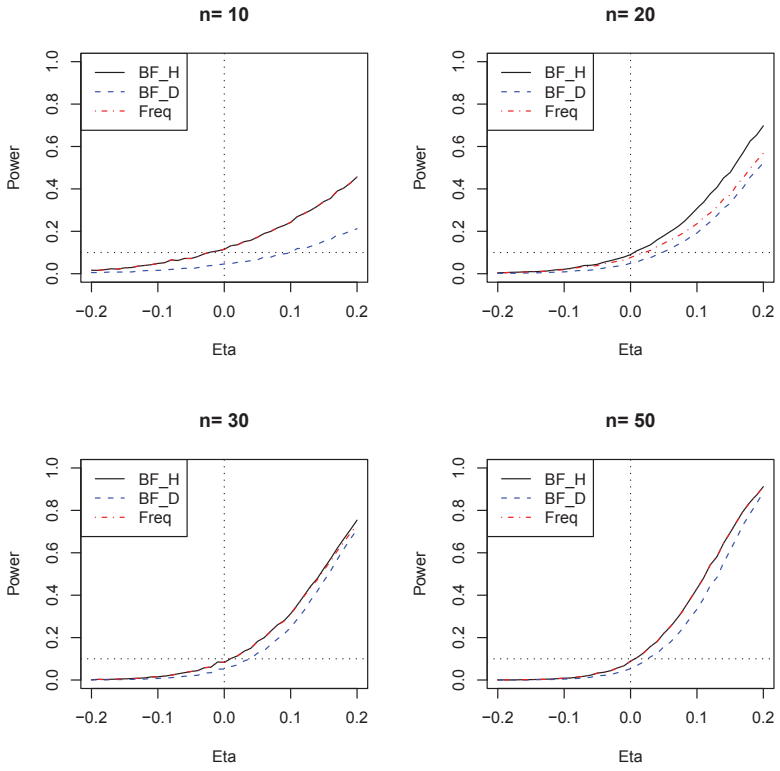
  when the priors are balanced, i.e., $\boldsymbol{w_1}^T A \boldsymbol{w_2} \approx 0.5$

Numerical Illustrations

- We first illustrate simulated data scenarios:
  $X_1|\theta_1 \sim Bin(n_1, \theta_1)$ and $X_2|\theta_2 \sim Bin(n_2, \theta_2)$
- True values:
  Control group: $\theta_1 \in \{0.3, 0.5, 0.8\}$, and
  Experimental group: $\theta_2 = \eta + g(\rho, \theta_1)$
  where $g(\rho, \theta_1) = \frac{\rho\theta_1}{1+\rho\theta_1-\theta_1}$ and $\eta \in [-0.2, 0.2]$ (with 0.01 increment)
- Thus, $\eta < 0$ favour the H_0, while positive values favour H_1
- Sample sizes: $n = n_1 = n_2 \in \{10, 20, 30, 50\}$
- Non-inferiority margin: $\rho = (odds(\theta_0)/odds(\theta_1))^{\epsilon}$ where $\theta_0 = \theta_1/2$ and $\epsilon = 0.2$ (see Ng, 2008)
- Compared against Blackwelder type test with 10^4 replicates



$\alpha = 0.05$



$\alpha = 0.10$

Streptococcal Pharyngitis Trial

- Patients with documented group A beta–haemolytic streptococcal pharyngitis were randomized to:
  - 500 mg twice daily erythromycin (standard treatment)
  - 250 mg twice daily clarithromycin (experimental treatment)
- The scientific question of interest:
  Is clarithromycin non-inferior to erythromycin in efficacy?
- The study patients are selected to 65 or younger from a single-center, unblinded, phase IV trial
- $X_1 = 97$ out of $n_1 = 107$ patients in the *erythromycin group* were observed to have symptoms cured or improved
- $X_2 = 98$ out of $n_2 = 106$ patients in the *clarithromycin group* were successfully treated

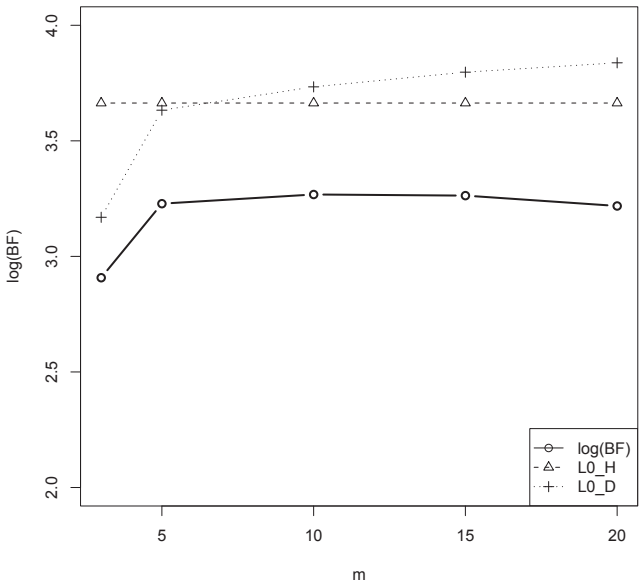
- Following Wellek (2003) and Siqueira et al. (2008), we carried out the following tests:

$$H_0 : \frac{\theta_2(1-\theta_1)}{\theta_1(1-\theta_2)} \leq \rho \text{ vs. } H_a : \frac{\theta_2(1-\theta_1)}{\theta_1(1-\theta_2)} > \rho$$

  θ_1: the success rate for patients receiving erythromycin
  θ_2: the success rate for the clarithromycin group

- The noninferiority margin $\rho = 0.5$ and the size of test $\alpha = 0.025$
- Used TWE with $w = 1 - \alpha$ (so that $AE_1 \leq \alpha$) and $m = 20$
- $\log[BF] = 3.218$ with cutoff value (minimizing TWE) $t_0 = 3.664$
- Accordingly, we failed to reject the null hypothesis, hence *noninferiority can not be claimed for clarithromycin*
- These results are consistent with the ones obtained by the frequentist methods (e.g., p-value$= 0.029$ based on the Blackwelder-type test)

Sensitivity with respect to the choice of m:



R package: BayesNI

Download the package from CRAN site:

https://cran.r-project.org/web/packages/BayesNI/

```
> install.packages("BayesNI")
> library(BayesNI)
> help.start()
> bayesNI(x1=97,x2=98,n1=107,n2=106,dm='OR',rho=0.5,m=20,
zeta=0.025,TWE=1)
H0:odds(theta2)/odds(theta1)<= 0.5 vs. H1:odds(theta2)/odds(theta1)>0.5
weight assignment in TWE: 0.975 Type I Error | 0.025 Type II error
logBF(x1,x2)= 3.2181 L0= 3.6635

$logBF
          [,1]
[1,] 3.218111
```



```
$L0
[1] 3.663562

$w1
 [1]  3.47e-01  0.00e+00 -2.11e-18  0.00e+00  2.20e-02
 [6]  9.23e-02  0.00e+00  0.00e+00  0.00e+00  0.00e+00
[11]  7.63e-02  0.00e+00  0.00e+00  0.00e+00  0.00e+00
[16]  9.24e-02  2.21e-02  0.00e+00 -2.12e-18  0.00e+00
[21]  3.47e-01

$w2
 [1]  3.47e-01  0.00e+00 -2.11e-18  0.00e+00  2.20e-02
 [6]  9.23e-02  0.00e+00  0.00e+00  0.00e+00  0.00e+00
[11]  7.63e-02  0.00e+00  0.00e+00  0.00e+00  0.00e+00
[16]  9.24e-02  2.21e-02  0.00e+00 -2.12e-18  0.00e+00
[21]  3.47e-01
```

```
> bayesNI(x1=97,x2=98,n1=107,n2=106,dm='OR',rho=0.5,m=10,
zeta=0.025,TWE=1)
H0:odds(theta2)/odds(theta1)<=0.5 vs. H1:odds(theta2)/odds(theta1)>0.5
weight assignment in TWE: 0.975 Type I Error | 0.025 Type II error
logBF(x1,x2)= 3.26787 L0= 3.6636

> bayesNI(x1=97,x2=98,n1=107,n2=106,dm='RD',rho=0.05,m=10,
zeta=0.025,TWE=1)
H0: theta2<=theta1- 0.05 vs. H1: theta2>theta1- 0.05
weight assignment in TWE: 0.975 Type I Error | 0.025 Type II error
logBF(x1,x2)= 2.9540 L0= 3.6636

> bayesNI(x1=97,x2=98,n1=107,n2=106,dm='RR',rho=0.95,m=10,
zeta=0.025,TWE=1)
H0: theta2/theta1<= 0.95 vs. H1: theta2/theta1> 0.95
weight assignment in TWE: 0.975 Type I Error | 0.025 Type II error
logBF(x1,x2)= 2.8545 L0= 3.6636
```


Relevant papers:

Reyes, E. M. and Ghosh, S. K. (2013). Bayesian Average Error Based Approach to Sample Size Calculations for Hypothesis Testing, Journal of Biopharmaceutical Statistics, 23, 569-588.

http://www.tandfonline.com/doi/abs/10.1080/10543406.2012.755994

Osman, M. and Ghosh, S. K. (2011). Semiparametric Bayesian Testing Procedure for Noninferiority Trials with Binary Endpoints, Journal of Biopharmaceutical Statistics, 21, 920-937.

http://dx.doi.org/10.1080/10543406.2010.544526

THE END

of PART I & II

THANKS!

Dhanyavaad धन्यवाद

For questions and collaborations contact me at

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