PREDICTIVE POWER FOR TWO BINOMIAL POPULATIONS IN CLINICAL TRIALS

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ABSTRACT

The Bayesian approach involves synthesising data and judgement in order to reach conclusions about unknown quantities and make predictions. In recent years, many authors have stressed the interest of the Bayesian predictive approach for designing and monitoring experiments. In the planning and design of new clinical trials, the calculation of the sample size and power is an essential part of the process. Power calculations are usually based on the estimated quantities of the analysis of historical data and are therefore subject to uncertainty. In many cases, this is addressed by the sensitivity analysis but simple sensitivity analysis provides an incomplete picture of the uncertainty of estimates of power. We describe here a Bayesian analysis of historical data in clinical trials using the binary data with a prior beta (a, b), which gives by the generation of the power distribution of a fully probabilistic predictive description of uncertainty in computing power.

Keywords: *Design, Bayesian analysis, power, clinical trials, binary data.*

1. INTRODUCTION

The Bayesian approach involves synthesising data and judgement in order to reach conclusions about unknown quantities and make predictions. Bayesian methods have become increasingly popular in recent years, notably in medical research, and although there are a number of books on Bayesian analysis, few cover clinical trials and biostatistical applications in any detail. Bayesian Approaches to Clinical Trials and Health-Care Evaluation provides a valuable overview of this rapidly evolving field, including basic Bayesian ideas, prior distributions, clinical trials, observational studies, evidence synthesis and cost-effectiveness analysis. Covers a broad array of essential topics, building from the basics to more advanced techniques such as predictive power.

Spiegelhalter et. al. (2004, see Section 6.5.5.) [1] give a simple explanation and example of the concept of a predictive power distribution. If the uncertainty about the quantities entering a conventional power calculation (for example mean values and standard deviation) is expressed in the form of prior distributions, then the predictive power can be considered simply as the distribution that is directly induced or implied by these priors: a function of the conditional power and the priors. Spiegelhalter et.al. Give an example of how this can be derived by Monte Carlo simulation in a simplified case (L. W. Huson. 2009 [2]) . This basic idea can be extended to include both prior belief about the uncertain quantities, and also information obtained from historical data, and then it becomes a fully Bayesian procedure. The predictive power distribution provides a complete summary of what a Bayesian would regard as being reasonable to believe about the study power. Provide a more detailed theoretical discussion of the use and interpretation of predictive power distributions.

It is natural to ask in the middle of a trial how likely it is that the trial will reach a conclusion or another, or even to reach any conclusion at all. Predictive probabilities provide a mechanism to address this issue. Predictive probabilities are easier to understand in the context of binary outcomes. This paper focuses on binary outcomes, although the same principles apply more broadly to other outcomes, such as the time of the event, (Satoshi Teramukai,a, Takashi Daimonb and Sarah Zoharc, 2012, [3])

the plan of this paper is as follows: in the next section we make the methodology with a prior beta (a, b) in Section 3 is given annually function predictive power with calculation posterior distribution, we simulated this function by matlab software with illustration a clinical phase II trial in section 4, we finally conclude with a discussion in Section 5 and conclusion in section 6.

2. METHODOLOGY

2.1 Bayesian sample size criteria for binomial parameters

Sample size determination for accurate estimation of a binomial parameter is arguably the most common design situation faced by statisticians.

Bayesian sample size methods use prior information about the binomial parameter rather than a point estimate, and fully account for the uncertainty in the predicted data (Cyr E. M'Lan 2008[4]).

Let *p* be the binomial parameter to be estimated based on a sample size of n, we assume the following prior-likelihood model: $p \sim Beta\ (a, b)$, a, b > 0, where *Beta (a, b)* indicates a beta distribution with parameters a and b :$\pi(p) = \frac{1}{B(a,b)} p^{a-1}(1-p)^{b-1} \quad 0 \le p \le 1$, and $x|p \sim Bin\ (n, p)$, n ≥ 2, *Bin (n, p)* represents the binomial distribution, with parameters *n* and *p*. As a result, the marginal predictive distribution of *x* is Beta-Binomial with

$$p(x/n, a, b) = \frac{B(a+x, b+n-x)}{B(a,b)}$$

For a given sample data point *x*, the posterior distribution of *p*, $\pi(p/x, n, a, b)$, is $B(a+x, b+n-x)$.

$$\pi(p/x) = \frac{p^{a+x-1}(1-p)^{b+n-x-1}}{B(a+x, b+n-x)} = Beta(a+x, b+n-x)$$

2.2 Prediction in clinical trials

A major strength of the Bayesian approach is the ease of making predictions concerning the events of interest. Examples of useful predictions: The probability of either success or futility if the trial is continued, Predictive probability of trial success under a given design, The probability that a given patient in the trial will respond to a given treatment, The probability that a future patient will respond to a given treatment.

We might want to evaluate a design or stopping decision based on the predictive probability of the number of total patients (inside and outside the trial) who get the superior treatment. We balance the needs of current and future patients.

Prediction provides discipline and pragmatic importance to empirical research. (Gary Koop, Dale J. Poirier, and Justin L 2007, [5] and (BERRY S. M, CARLIN B.P., LEE J.J, MULLER P. 2011[6])..) Suppose a deity told you the values of all unknown parameters in your model so that estimation and hypothesis testing became moot. What would you do with your model? The obvious answer is to use it for what it is intended to do: Make ex ante probability statements about future observables. Suppose the information set consists of the union of past data $Y = y$, yielding the parametric likelihood function $L(\theta)$, and other information in the form of a prior distribution $p(\theta)$. The sampling distribution of an out-of-sample Y_* (possibly a vector) given $Y = y$ and θ would be an acceptable predictive distribution if θ were known, but without knowledge of θ it cannot be used. Then the Bayesian predictive probability distribution $p(y_*|y)$ is

$$\begin{aligned} p(y_* \backslash y) &= \frac{p(y_*, y)}{p(y)} \\ &= \int_\Theta \frac{p(y_*, y, \theta)}{p(y)} d\theta \\ &= \int_\Theta p(y_* \backslash y, \theta) \left[\frac{p(\theta) p(y \backslash \theta)}{p(y)}\right] d\theta \\ &= \int_\Theta p(y_* \backslash y, \theta)\ p(\theta \backslash y) d\theta \\ &= E_{\theta \backslash y}\left[p(y_* \backslash y, \theta)\right]. \end{aligned}$$

2.3 The Predictive Power Approach

Many authors have advocated calculating the "predictive power", averaging conditional power over values of *p* in a Bayesian calculation. We are led to a Bayesian approach, but still with a frequentist test in mind. Formally, the prediction uses the posterior distribution of *p*, given a prior and the data available at the interim analysis. For the inference about a proportion, the calculations are particularly simple if we choose a conjugate Beta prior distribution (Lecoutre et al., 1995 [7]):

Prior: $p \sim Beta\ (a, b)$

Posterior: $p/x \sim Beta\ (a+x, b+n_1 - x)$

Predictive: y |x~ Binomial-Beta $(a+x, b+n_1 - x; n)$

Assume that $X \sim B(n, p)$ and $p \sim Beta(a, b)$. At the first stage with n_1 subjects, the posterior distribution of p given X is given by

$$\pi_1(p|x) = Beta(a + x, b + n_1 - x) \quad (1)$$

Similarly, at the end of the second stage with n subjects, the posterior distribution of p given X is

$$\pi(p|x) = Beta(a + x, b + n - x) \quad (2)$$

For testing the null hypothesis that $H_0 : \theta \leq 0$ against an alternative hypothesis that $H_1 : \theta > 0$, we defined the Bayesian significance as

$$P_B = P(\theta < 0 | \text{data}) < \alpha_B.$$

As a result, the cutoff point for stopping the trial is chosen in a way such that the Bayesian power at the first stage is $(1-\beta_1)$ at Bayesian significance level of α_{β_1}. Similarly, the n is chosen such that the Bayesian power at the second stage is $(1-\beta)$ at Bayesian significance level α_B (Shein Chung Chow Mark Chang, 2007[8])]). Based on (1) and (2), conditional power and predictive power can be derived. Given X out of n_1 patients who respond at the first stage, the probability (or conditional power) of having at least y additional responses out of the n_2 additional patients at the second stage is given by:

$$p(y/x, n_1, n_2) = \sum_{i=y}^{n_2} \binom{n_2}{i} \left(\frac{x}{n_1}\right)^i \left(1 - \frac{x}{n_1}\right)^{n_2 - i} \quad (3)$$

As a result, the predictive power or the predictive probability of having at least y responders out of additional m patients, given the observed response rate of x/n_1 at the first stage:

$$p(y\backslash x, n_1, n_2) = \int_0^1 p(Y \geq y \backslash p, n_2) \;\; \pi(p\backslash x) dp$$

$$= \int_0^1 \sum_{i=y}^{n_2} \binom{n_2}{i} p^i (1-p)^{n_2 - i} \frac{p^{a+x-1}(1-p)^{b+n_1-x-1}}{B(a+x, b+n_1-x)} dp \quad (4)$$

$$p(y/x, n_1, n_2) = \sum_{i=y}^{n_2} \binom{n_2}{i} \frac{B(a+x+i,\; b+n_1+n_2-x-i)}{B(a+x, b+n_1-x)} \quad (5)$$

3. SIMULATIONS

3.1 Simulation setting

In this section, we calculate the formula (5) with Matlab, for a good illustration, we consider a phase II study, hypotension comparing a test treatment with an active control agent. Assuming that the sample size for the first stage, n_1 =23, the size of the sample for the second step, n_2= 20, at a given time, x = 16 responses and the treatment effect is estimated distribution of beta (a, b).

3.2 Simulation results

3.2.1 Calculation of predictive power with uniform prior

x = 16, n_1 =23, n_2 = 20, a=b=1

Table.1. Calculation of predictive power with *uniform prior*

trials	Y	$p(y/x, n_1, n_2)$
1	1	0.0000006
2	2	0.0000048
3	3	0.0002385
4	4	0.0009130
5	5	0.0028836
6	6	0.0078103
7	7	0.0186020
8	8	0.0396457
9	9	0.0765646
10	10	0.1352247
11	11	0.2199210
12	12	0.3310849
13	13	0.4633414
14	14	0.6050448
15	15	0.7402081
16	16	0.8528441
17	17	0.9323519
18	18	0.9774064
19	19	0.9958497
20	20	0.9999994

3.2.2 Calculation of predictive power with non informative Jeffreys prior:

x = 16, n_1 =23, n_2 = 20, a=b=0.5

Table.2. Calculation of predictive power with non informative Jeffreys prior

trials	Y	$p(y/x, n_1, n_2)$
1	1	0.0000006
2	2	0.0000048
3	3	0.0002385
4	4	0.0009130
5	5	0.0028836
6	6	0.0078103
7	7	0.0186020
8	8	0.0396457
9	9	0.0765646
10	10	0.1352247
11	11	0.2199210
12	12	0.3310849
13	13	0.4633414
14	14	0.6050448
15	15	0.7402081
16	16	0.8528441
17	17	0.9323519
18	18	0.9774064
19	19	0.9958497
20	20	0.9999994

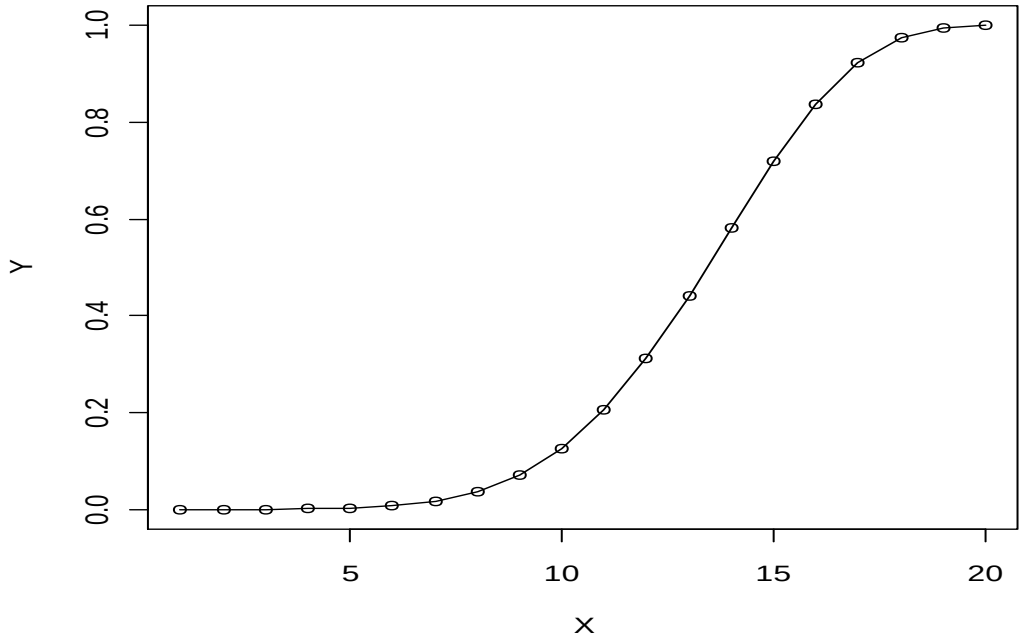

Figure.1. Distribution of predictive power with uniform prior, a=b=1

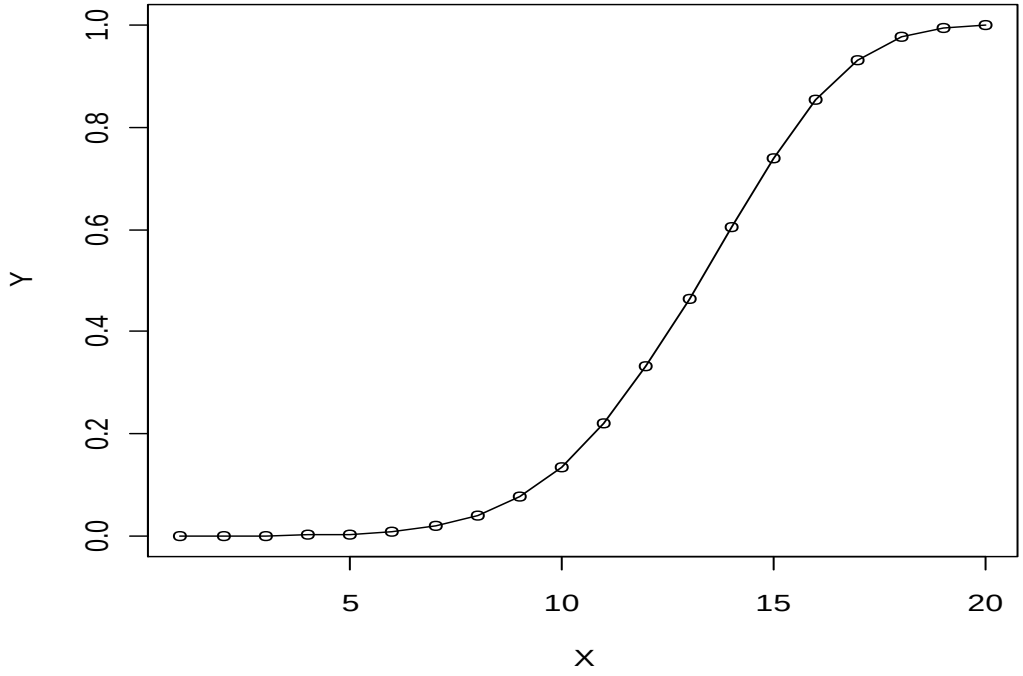

Figure.2. Distribution of predictive power with non informative Jeffreys prior, a=b=0.

4. SUMMARY OF SIMULATION RESULTS

The Bayesian process, instead of producing a single point estimate of power for the new clinical trial, yields a predictive (or posterior) distribution which summarizes the uncertainty about the power of planned new trial, and shows plausible values for this power. The predictive power distribution derived using the Bayesian binary data is summarised in Figure 1 and Figure 2:

- After the first table with uniform prior, beta (1, 1) and x= 16, n_1 =23, n_2 = 20, the predictive likelihood or predictive power in the final trial with $y = 20$, $p(y/x) = 0.9999995$

-In the second case with non informative Jeffreys prior, beta (0.5, 0.5) and $x = 16$, $n_1 = 23$, $n_2 = 20$, the predictive power, $y=20$, $p(y/x)=0.9999994$.

We can conclude from these two tables: the predictive power increases and converges to 1.

5. CONCLUSIONS

The use of Bayesian predictive power analysis is sometimes regarded as a curious mixture of Bayesian and Frequentist philosophies. The "uncertain quantity" which is being estimated is the study power, and the power of a study is a firmly frequentist concept. The Bayesian analysis tells us, in effect, what degree-of-belief to attach to any particular range of estimated power values. Predictive power analysis appears still to be little used in practice, and one of the reasons for this may be that a conventional Bayesian analysis must either use analytical techniques, which in most cases, for reasons of tractability, severely restricts the distributional assumptions which can be made, or must make use of specialist Bayesian software's such as the R, Win BUGS, Matlab,...

The main advantage of the Bayesian the binary data with a priori beta (a, b) technique is that it is computationally simple to implement and can easily be programmed in most packages and with most programming languages. This makes it an attractive option for commonly performed calculations such as power analyses (Chow S.C., J.(2008)[9]). The results reported here show that, for this example at least, the predictive power distribution from the Bayesian binary data is very similar to that produced from a more conventional Bayesian analysis using R.

Predictive power analysis is not the only Bayesian approach to determination of sample size and power. A convenient summary of some of the alternative Bayesian methods is given by (Chow et. al. (2008) [10]. More detailed descriptions of other methods – some quite different from the one presented here - are also given by Grouin et. al. (2007) [11]) and Pezeshk (2003) [12].

6. REFERENCES

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