BAYESIAN PREDICTION IN CLINICAL TRIALS DESIGN

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Abstract

The aim of an exploratory clinical trial is to determine whether a new intervention is promising for further testing in confirmatory clinical trials. Most exploratory clinical trials are designed as single-arm trials using a binary outcome with or without interim monitoring for early stopping. In this paper, we are particularly interested in using the predictive Bayesian approach in clinical trials or objectives is the development of important evidence of an effect of interest we offer the procedure based on the notion satisfaction Index is based on the value of p and we are first given the data available to calculate a forecast of future satisfaction data as Bayesian predictive expect this index conditional on past observations. To illustrate the proposed procedure, we proposed the binomial model.

Keywords: Bayesian statistics, predictive methods, clinical trials, binomial model.

Introduction:

The aim of exploratory clinical trials, such as phase II trials and proof-of-concept studies, is to determine whether a new intervention is promising for further testing in confirmatory clinical trials, such as phase III randomised controlled trials. Most exploratory clinical trials are designed as single-arm trials with or without interim monitoring for early stopping. In this setting, the efficacy of treatment is commonly evaluated using a binary outcome such as tumour shrinkage or response to treatment (Satoshi Teramukai,a, Takashi Daimonb and Sarah Zoharc, 2012). Bayesian approaches are ideal for such exploratory clinical trials as they take into account previous information about the quantity of interest as well as accumulated data during a trial. The clinical trial, a prospective study to evaluate the effect of interventions in humans under prespecified conditions, is a standard and integral part of modern medicine. Many adaptive and

sequential approaches have been proposed for use in clinical trials to allow adaptations or modifications to aspects of a trial after its initiation without undermining the validity and integrity of the trial. The application of adaptive and sequential methods in clinical trials has significantly improved the flexibility, efficiency, therapeutic effect, and validity of trials (Ton J Cleophas, Aeilko H Zwinderman and Toine F Cleophas, 2009).

Prediction models are important in various fields, including medicine, physics, meteorology, and finance. Prediction models will become more relevant in the medical field with the increase in knowledge on potential predictors of outcome, e.g. from genetics. Also, the number of applications will increase, e.g. with targeted early detection of disease, and individualized approaches to diagnostic testing and treatment. The current era of evidence-based medicine asks for an individualized approach to medical decision-making. Evidence-based medicine has a central place for meta-analysis to summarize results from randomized controlled trials; similarly prediction models may summarize the effects of predictors to provide individualized predictions of a diagnostic or prognostic outcome, (Steyerberg, E.W, 2009)

In this paper we consider the prediction within the experimental design for this, we define a hypothesis is defined indices of satisfaction and anticipation of satisfaction related to a test as a decreasing function of the p-value, satisfaction is higher than the null hypothesis is rejected wider, that is to say, the p-value is small. We consider the case of a two-step procedure, which is often done in the case of clinical trials where these satisfaction indices are interesting protocols and when the inference concerns an effect evaluated from the future sample. We treated our applications given by software: Matlab and R.

The outline of the paper is as follows.. Section 2 introduces the basic idea of prediction in experimental design. In section 3, we propose a study predictive sue the binomial model, we present an illustrative example and conclude with a discussion in Section 4.

Prediction in the experimental design:

- Choice of model

Specify the experimental context that consists of two successive experiments, results $\omega' \epsilon \Omega'$ and $\omega \epsilon \Omega$, which are usually conducted independently. Laws depend in a well established model, parameter $\theta \epsilon$; only ω'', in the case of the experimental design used to build the official conclusion of the study and determine the user satisfaction it will be appreciated $\emptyset(\omega'')$. But it is worth, based on the result of ω' the first phase, to predict what will be the satisfaction at the end of the second phase. In our study, (Christian P, Robert and George Casella, 2007), this prediction is

performed in a Bayesian framework, that is to say, based on the choice of a priori probability of ⭘.It notes:

$P_{\Theta\times\Omega'\times\Omega''}$: Probability of $\Theta\times\Omega'\times\Omega''$,

P_{Θ}: A priori probability of ⭘

$P_{\Theta}^{\omega'}$: A posteriori probability of θ, based on the result of the first phase.

$P_{\Omega''}^{\theta}$: Law sampling of the 2nd phase

$P_{\Omega''}^{\omega'}$: Probability of Ω" conditioned by the result of the first phase of ω' (not to be confused, of course $P_{\Omega''}^{\theta,\omega'}$, with that, because at θ fixed, the two experiments are independent, is none other than $P_{\Omega''}^{\theta}$).

Recall that, according to the usual Bayesian terminology (Christian P, Robert and George Casella, 2004), we call predictive probability on the probability $P_{\Omega'\times\Omega''}$ space complete results.

This will help us later on Ω' is the probability "that follows by conditioning by ω'.

We propose to associate with any satisfaction index on the second phase of an index forecasting is the expectation with respect $P_{\Omega''}^{\omega'}$. In other words, what will be of interest to potential users of the indicator of satisfaction $\emptyset(\omega'')$, that is, after the first phase, the prediction of the average value knowing ω'. Recall that the predictive probability is a valuable tool for planning and conducting an experiment for reasons of ethical concerns or because the treatment is particularly toxic and expensive,
(BERRY S. M, CARLIN B.P., LEE J.J and MULLER P, 2011).

- Index and prediction of satisfaction:

We define the indices of satisfaction and anticipation of satisfaction related to a decreasing hypothesis test as a function of the p-value, satisfaction is higher than the null hypothesis is rejected more broadly, that is to say that p-value is small. We consider the case of a two-step procedure, which is often done in the case of clinical trials where these satisfaction indices are interesting protocols and when the inference concerns an effect evaluated from the future
sample only.

Consider the satisfaction provided by the second phase of the experiment and the predicted using the first. We saplings under which the statistician "wants" to observe a significant result, i.e. reject the null hypothesis Θ_0. His "satisfaction" will be greater in the case of rejection, and even generally much larger than the observation that led to the rejection is more significant.

Being fixed α, a level α test defined by the critical first satisfaction index region $\Omega_1^{"(\alpha)}$ the study in (Merabet, H, 2004):

$$\emptyset(\omega") = 1_{\Omega^{"(\alpha)}}(\omega")$$

The default index above that expresses satisfaction "all or nothing". It is interesting to consider to what extent the result will always appear significant. Therefore a new level of satisfaction defined is used:

$$\emptyset(\omega") = 0 \; si \; \omega" \epsilon \Omega_0^{"(\alpha)}$$
$$= 1 - inf\left\{\beta;\ \omega" \epsilon \Omega_1^{"(\beta)}\right\} si \; \omega" \epsilon \Omega_1^{"(\alpha)}$$
$$=1\text{-p}$$

Recall that $\inf\left\{\beta;\ \omega" \epsilon \Omega_1^{"(\beta)}\right\}$ is what practitioners note the associated ω" and is called the p-value, it is considered a measure of credibility to be attached to the null hypothesis and practitioners often use to meet several critical and disadvantages of the approach Neymann -Pearson, you can see why. (Gary Koop, Dale J. Poirier, and Justin L , 2007) Therefore, the more that p is, the more the practitioner Considers that the result is significant.

An indicator of prediction is given by:

$$\pi(\omega') = \int_{\Omega_1^{"(\alpha)}} \emptyset(\omega") P_{\Omega"}^{\omega'}(d\omega") \qquad (1)$$

$$= \int_{\Theta} \left(\int_{\Omega_1^{"(\alpha)}} \emptyset(\omega") P_{\Omega"}^{\theta}(d\omega") \right) P_{\Theta}^{\omega'}(\theta) \qquad (2)$$

Note that $\int_{\Omega_1^{"(\alpha)}} \emptyset(\omega") P_{\Omega"}^{\omega'}(d\omega")$ generalizes the power of the test in the logic of satisfaction index proposed and is different from insurance introduced in (O'.HAGAN A, STEVENS J.W, CAMPBELL M.J, 2005) and it is the practitioner to decide below which value Satisfaction Index, he gave up the pursuit of experience.

Application

We propose to calculate the prediction of satisfaction in several models where the law of the unknown parameter θ is a conjugate prior or uninformative and we predictive approach. The sequential aspect of treatment that will be adopted is a particularly innovative element relative to existing technology; it helps to alleviate the most ambitious multi-phase studies that the existing, more licensed statistical analysis, a patient both, is ethical because it allows a stop shorter and less late experience.

We denote θ the probability that an individual suffering from a disease is cured with M from a treatment t (consisting of the administration of a drug).

To estimate the unknown parameter θ, T is administered to patients the treatment t. there $x_i \epsilon \{0,1\}$, i the patient following administration of treatment t; x_i= 1 if the patient *i* is cured and x_i= 0 otherwise. It is also considered that the medication (treatment related t) may be marketed only if $\theta \geq \theta_0$. From a statistical point of view (Shein Chung, 2007), we can formulate the problem using the following test:

$H_0: \theta \leq \theta_0$

We work in the framework of the sampling model where we assume that are realizations of independent random variables X_i and even Bernoulli parameter θ, again for the sake of completeness we take $\omega' = \sum_{i=1}^{T} x_i$. . If we choose as prior distribution for θ a beta law $B(\underline{\alpha}, \underline{\delta})$ is then known that the posterior distribution of $\theta/_{\omega'}$ is still a beta law $B(\overline{\alpha}, \overline{\delta})$ with $\overline{\alpha} = \underline{\alpha} + \omega'$ and $\overline{\delta} = \underline{\delta} + T + \omega'$.

The satisfaction index for observation $\omega'' = 0$ or 1 is:

$$\emptyset(\omega'') = 0 \; si \; \omega'' < q_0 \quad (3)$$

$$= \sum_{s=0}^{\omega''-1} \theta_0^s \; (1-\theta_0)^{1-s} si \; \omega'' \geq q_0 \quad (4)$$

With

$$q_0 = inf\{u; \sum_{s=u}^{1} \theta_0^s \; (1-\theta_0)^{1-s} \leq \alpha\} \quad (5)$$

On the other hand, the predictive density $\omega''=\omega'$ is none other than the beta-binomial

$$f(\omega''/\omega') = \int_0^1 f(\omega''/\theta) f(\theta/\omega') d\theta \quad (6)$$

$$= \int_0^1 \theta^{\omega''} (1-\theta)^{(1-\omega'')} \left[B(\overline{\alpha}, \overline{\delta})\right]^{-1} \theta^{\overline{\alpha}-1} (1-\theta)^{\overline{\delta}-1} d\theta \quad (7)$$

$$= \left[\frac{\Gamma(\overline{\alpha}+\omega'') \, \Gamma(\overline{\delta}+1+\omega'')}{\Gamma(\overline{\alpha}+\overline{\delta}+1)}\right] \left[\frac{\Gamma(\overline{\alpha}+\overline{\delta})}{\Gamma(\overline{\alpha})\Gamma(\overline{\delta})}\right] \quad (8)$$

Predicting satisfaction is given by:

$$\pi(\omega') = \sum_{\omega''=q_0}^{1} \sum_{s=0}^{\omega''-1} \theta_0^s \; (1-\theta_0)^{1-s} \left[\frac{\Gamma(\overline{\alpha}+\omega'') \, \Gamma(\overline{\delta}+1+\omega'')}{\Gamma(\overline{\alpha}+\overline{\delta}+1)}\right] \left[\frac{\Gamma(\overline{\alpha}+\overline{\delta})}{\Gamma(\overline{\alpha})\Gamma(\overline{\delta})}\right]$$

Note that we can generalize a plan experience where $\omega'' = \sum_{i=1}^{T'} x_i$ and the Binomial model is found. The satisfaction index is:

$$\emptyset(\omega'') = 0 \; si \; \omega'' < q_0 \quad (9)$$

$$= \sum_{s=0}^{\omega''-1} \binom{T'}{s} \theta_0^s (1-\theta_0)^{T'-s} \; si \; \omega'' \geq q_0 \quad (10)$$

or

$$q_0 = inf\left\{u, \sum_{t=u}^{T'} C_{T'}^{t}\ \theta_0^t(1-\theta_0)^{T'-t} \le \alpha\right\}.$$

The predictive density is:

$$f(\omega''/\theta) = \int_0^1 f(\omega''/\theta)\, f(\theta/\omega')d\theta \quad (11)$$

$$=\int_0^1 \binom{T'}{\omega''} \theta^{\omega''}(1-\theta)^{(T'-\omega'')}\left[B(\overline{\alpha},\overline{\delta})\right]^{-1}\theta^{\overline{\alpha}-1}(1-\theta)^{\overline{\delta}-1} \quad (12)$$

$$=\binom{T\prime}{\omega''}\frac{\left[B(\overline{\alpha},\omega'',\overline{\delta}+T\prime-\omega'')\right]}{\left[B(\overline{\alpha},\overline{\delta})\right]} \quad (13)$$

We deduce index prediction is different from the predictive power given by:

$$\pi(\omega') = \sum_{\omega''=q_0}^{T''} \sum_{s=0}^{\omega''-1}\binom{T'}{s}\theta_0^s\ (1-\theta_0)^{T''-s}\left[\binom{T''}{\omega''}\frac{\Gamma(\overline{\alpha}+\omega'')\,\Gamma(\overline{\delta}+T''+\omega'')}{\Gamma(\overline{\alpha}+\overline{\delta}+T'')}\right]\left[\frac{\Gamma(\overline{\alpha}+\overline{\delta})}{\Gamma(\overline{\alpha})\Gamma(\overline{\delta})}\right] \quad (14)$$

For example: Suppose two imaging modalities (e.g., CT vs.MRI) for diagnosing lung cancer are to be compared on the basis of test accuracy (sensitivity, specificity, and the area under the ROC curve).

Suppose $T=T'$ =20 are the sample sizes of the two groups and the prior probability of the null hypotheses is p=0.5. The predictive probability at each point $\pi(\omega')$ is calculated via simulation, similar to that given by Equation (14) with:

1. a = b = 0.5

scenario	ω'	$\pi(\omega')$
1	0	0.00000006
2	1	0.000005
3	2	0.000015
4	3	0.000076
5	4	0.00031
6	5	0.00108
7	6	0.00314
8	7	0.00797
9	8	0.01807
10	9	0.0371
11	10	0.0701
12	11	0.1221
13	12	0.1977
14	13	0.2987
15	14	0.4220
16	15	0.5591
17	16	0.6957
18	17	0.8153
19	18	0.9040
20	19	0.9559
21	20	0.9765

TableI: prediction with a = b = 0.5

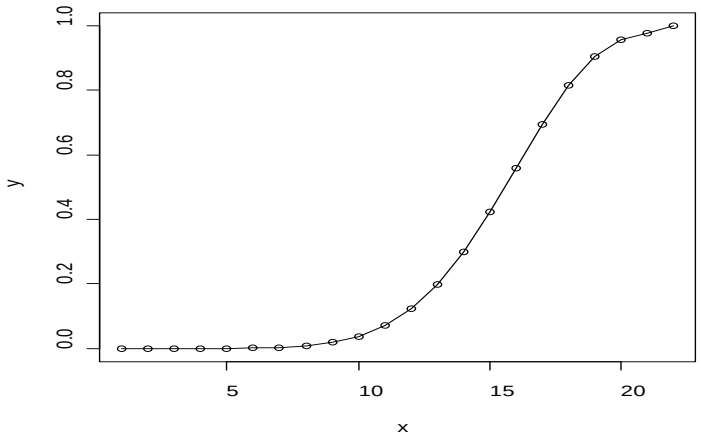

Figure. I: the graphical presentation of prediction

We note in Table I, where ω' is included in [0, 17], the result of p = 0.5 varies from 0.00000006 to 0.8153. Therefore we conclude $H_0$for Y <17. On the other hand, when ω' is included in [18, 20] the result p varies from 0.9040 to 0.9765. In this case, instead of deciding for H_1 considering the predictive probability is the weighted average of the indicator of a test which runs until the end of the study.

2. a=b=1

Scenario	ω'	$\pi(\omega')$
1	0	0.0000007
2	1	0.000006
3	2	0.00002
4	3	0.00010
5	4	0.00039
6	5	0.00125
7	6	0.0034
8	7	0.0083
9	8	0.0183
10	9	0.0367
11	10	0.0679
12	11	0.1166
13	12	0.1869
14	13	0.2809
15	14	0.3965
16	15	0.5269
17	16	0.6602
18	17	0.7818
19	18	0.8779
20	19	0.9404
21	20	0.9708

***Table. II*:** Representation of prediction with a = b = 1

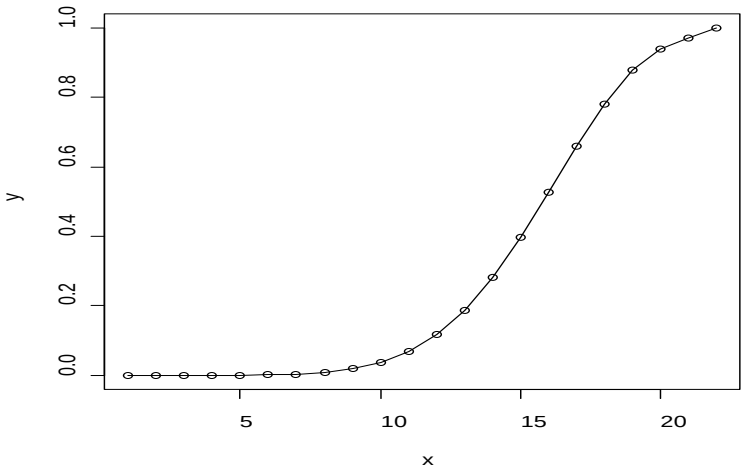

Figure. II*:* Graphical representation of prediction with a = b = 1

We note in Table II where ω is included in [0, 18], the result of p = 0.5varies from 0.0000007 to 0.8153. Therefore we conclude H_0 for Y <18. On the other hand, when ω is included in [18, 20] the result p varies from 0.9040 to 0.9765. In this case, instead of deciding for H_0 considering the predictive probability is the weighted average of the indicator of a test which runs until the end of the study.

As can be concluded from two tables when the parameters of the beta law are equal and equal to 0.5 and the value of p = 0.5 we get the best convergence predictive probability.

Conclusion

The aim of our work was to propose a simple Bayesian adaptation in experimental trials , considered the procedure based on fulfillment of the prediction index concept design , we believe that we can say that the Bayesian predictive approach proposed can be used to predict on the basis of statements frequentist results, we nevertheless believe that the frequentist approach sheds a different light on data and should not be excluded from further our goal is to develop an effective and flexible design that has desirable statistical properties .

The prediction can also be made to approach the frequentist derivatives resulting from the Bayesian approach. We have improved the methodology in the design of clinical trials by providing a prediction indices in a Bayesian framework, as is always the case in the clinical trial protocol and we illustrate our results using the binomial model.

We conclude that the predictive probability approach for interim control is a coherent, effective and flexible method that more closely resembles the process of clinical decision making .

References:

BERRY S. M, CARLIN B.P., LEE J.J, MULLER P, Bayesian Adaptive Methods for Clinical Trials. Chapman & Hall/CRC biostatistics series, 2011.

Christian P, Robert and George Casella, Monte Carlo Statistical Methods, Springer, 2004.

Gary Koop, Dale J. Poirier, and Justin L. Tobias, Bayesian econometric methods, 2007

Lyle D.Broemeling, Bayesian Biostatistics and Diagnostic Medicine. Chapman & Hall/CRC, 2006.

Merabet, H, Index and prevision of satisfaction in exponential models for clinical trials. STATISTICA, anno LXIV, n.3, 441-453, 2004.

O'.HAGAN A, STEVENS J.W, CAMPBELL M.J., Assurance in clinical trial design,pharmaceut;Statist,4,187-201, 2005.

Shein Chung Chow Mark chang, Adaptive design methods in clinical trials, Chapman & Hall/CRC biostatistics series,2007.

Steyerberg, E.W. Clinical Prediction Models A Practical Approach to Development, Validation, and Updating, XXVIII, 500p, Hardcover, 2009.

Ton J Cleophas, Aeilko H Zwinderman, Toine F Cleophas, Statistics Applied to Clinical Trials, 1 vol. (XIX-559 p.): ill.; 25 cm, 2009.

Satoshi Teramukai,a, Takashi Daimonb and Sarah Zoharc, A Bayesian predictive sample size selection design for single-arm exploratory clinical trials, statistics in medicine, 2012.