The design and analysis of sequential clinical trials

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ملخص
هذا العمل هو تعميم منهجية ومنهجة للتجارب الطبية التطبيقية في إطار بايزي. كان علينا أن نستعمال جانب متسلسل بايزي بحت. توفر هذه المقالة حلا بايزي بالكامل يتضمن التنبؤ في إشكالية شاملة. في تحليل متوسط، الاستدلال التنبؤي يغطي كافة البيانات، المتاحة، فضلا عن البيانات في المستقبل، بهذه الطريقة، لا يتم المبالغة في تقييم الخطأ التنبؤي كنهج تأخذ في الاعتبار الامتثال في المستقبل . طبقنا الإجراءات المقترحة لنموذج قوس، تمكنا من التوصل إلى نموذج واضح لاحتمالات الخطأ المختلفة التي يمكن أن ترتكب من ممارس. هكذا نتمكن من توفير للمستخدم أداة للتنفيذ و بايزى بشكل كامل. الجانب التسلسلي للمعاملة المعتمدة في هذه الدراسة هو مبتكر بشكل خاص بالمقارنة مع التكنولوجيا الحالية، فإنه يسمح أيضا تخفيف دراسات مراحل متعددة أكثر طموحا من القائمة، الذي يجعل بالنسبة للمريض التحليل أكثر أخلاقية بحيث يسمح توقف التجربة قبل الأوان.

الكلمات المفتاحية : *الأساليب التنبؤية - التحليل البايزي - التجارب الطبية التطبيقية - القيمة .*

Résumé
Ce travail est une généralisation et une systématisation de la méthodologie pour les essais cliniques dans un cadre Bayésien. Nous avons pu utiliser un aspect séquentiel purement Bayésien. Cet article permet une solution intégralement Bayésienne qui incorpore la prévision dans une problématique globale. Dans une analyse intermédiaire, l'inférence prédictive porte sur l'ensemble des données, celles disponibles ainsi que les données futures, de cette manière, l'évaluation de l'erreur de prévision n'est pas surévaluée comme dans une approche qui ne prend en compte que l'observation future. Avec des procédures proposées au modèle gaussien, il a été possible d'aboutir à une forme explicite des diverses probabilités d'erreurs que peut commettre le praticien. Ainsi, nous pouvons proposer à l'utilisateur un outil implémentable et complètement Bayésien. L'aspect séquentiel du traitement adopté dans cet article est un élément particulièrement innovateur par rapport à la technologie existante, il permet aussi d'alléger des études multi phases plus ambitieuses que l'existantes, ce qui pour le patient rend l'analyse plus éthique puisque cela permet un arrêt de l'expérience moins tardif.

Mots Clés *: Méthodes Prédictives- Analyse Bayesienne- Essais Cliniques-p-Valeur.*

Abstract
This work is a generalization and systematization of the methodology for clinical trials in a Bayesian framework. We have used a purely Bayesian sequential aspect. This article provides a solution fully Bayesian that incorporates the prevision in a global issue. In an intermediate analysis, the predictive inference focuses on all the data, the data available and future data, in this manner, the evaluation of the prevision error is not overvalued as in an approach that does take into account the future observation. We applied the proposed procedures to the Gaussian model and it was possible to reach an explicit form of the various probabilities of errors that the practitioner can make. Thus we can make available to the user an implementable tool and fully Bayesian.
The sequential aspect of the treatment adopted in this paper is a particularly innovative element compared to existing technology; it also helps to reduce multiphase studies more ambitious than the existing, which for the patient makes the analysis more ethical since it allows a stoppage of the experience shorter and less tardy.

Key Words: *Predictive methods-Bayesian analysis-Clinical Trials-p-Value.*

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1. INTRODUCTION

We propose a unified methodology for sequential clinical trials under a Bayesian paradigm. The idea is to make predictive inference based on the data accrued so far together with future data, we describe the use of predictive probability in deciding whether to stop a clinical trial, in contrast to previous work [1, 2] where we considered only the future sample and this case came within the experimental design in clinical trials.
This work involves theoretical developments motivated by practical applications to clinical trials in pharmacology. The aim is to improve the traditional methodology (use of hypothesis testing) increasingly regarded as insufficient, by supplementing it with the use of satisfaction indices and prevision of satisfaction.
Convincing motivation is that the user of hypothesis testing is generally not satisfied with the brutal verdict (significant versus not significant) of these tests and wishes to obtain a more nuanced judgment. In this sense, this paper proposes solutions of interest easy to implement in practical and relatively easy to interpret for the users of statistical tests.
The main tool consists of the Bayesian predictive probabilities, whose theoretical and practical importance is increasingly recognized. It is indeed a key to calculate the predictive probabilities of future results [3].
The exemplary situation developed in this work is that where one has a first set of data (preliminary phase), which is used to determine whether the experimentation should be abandoned or otherwise should be continued with a real chance of success (if the experimenter is satisfied in a second phase demonstrator).
Based on the fact that most clinical trials meeting "legal" requirements (imposed by the control authorities for the authorization of placing drugs on the drug market) use as primary criterion of evaluation the significance level of a frequentist test, which is no else than the *p-value*. May we recall for this purpose that the *p-value* is always regarded as a measure of credibility to be attached to the null hypothesis that practitioners often use to answer several criticisms and disadvantages of the Neymann Pearson approach [4].

We propose to calculate an index of satisfaction which is a function of the level p which is zero in case of non-significant result. Given the available data, we can calculate a prevision of satisfaction for future data as the expected Bayesian predictive index conditional on previous observations. The Bayesian predictive probability turns out to be a complementary concept compared to that of the power and we recommend its use routinely for planning tests [5]. Its use may avoid the experimenters many illusions about the chances of actually reaching a desired conclusion.
Two families of limited and unlimited indices are defined and their predictive distributions in the exponential models are derived and studied in [1, 2]. Numerical applications were used to compare these indices with those proposed in the literature and also demonstrate the methodological interest of the approach.
The predictive probabilities can also be used for intermediate analyses. If, for example, we want to show the superiority of one treatment, it is essential to stop the trial as quickly as possible, either because we have sufficient evidence for the conclusion desired or mainly because we see that the treatment is ineffective. Intermediate analyzes are performed for which a predictive Bayesian approach has been proposed [6 - 8]. In an intermediate analysis, the predictive inference focuses on all the data (the available data and future data).
This work is a natural extension of previous work [1, 2] since it offers the practitioner a satisfaction made by both the first and second phase of the experiment in the case of a classical or Bayesian test study. It is predicted using first phase unlike early results where only the result of the second phase is to establish a formal conclusion of the study. We illustrate the procedure by applied to the Gaussian model.

2. STATISTICAL METHODOLOGY

2.1 Choice of model

The Statistical methodology has already been used by [9] and [10]. Recall that it is in this context that Brown *et al.* [9] and Grouin [11] proposed to introduce a Bayesian model. It is worth noting that this experimental model is choosing $(P_\theta)_{\theta\in\Theta}$ a family of probability measures over a space of observations Ω in which Θ is the space of the unknown parameter and let Θ_0 be the null hypothesis to be tested against the alternative assumption Θ_1. Let us specify this experimental context that consists of two successive experiments, of results $\omega'\in\Omega'$ and $\omega''\in\Omega''$, which are generally conducted independently. Their distributions depend, within the

framework of a well established model, of a parameter $\theta \in \Theta$; consider $\omega''' = (\omega', \omega'')$ rather than ω'' as is done in experimental planning, which this time will be used to establish the official conclusion of the study and determine the user satisfaction, we denote $\phi(\omega''')$. But it is worth, based on the result of the first phase ω', to predict what will be the satisfaction at the end of the first and second phase. The predictive probability of obtaining the desired conclusion is an important element to consider in the decision. A very high or very weak probability is an argument in favor of the interruption of the trial. In our study, as in [12], the prediction is performed within a Bayesian context, *i.e.*, based on the choice of a prior on Θ.

We consider the context in which the statistician "wishes" to observe a significant result, *i.e.*, to reject the null hypothesis Θ_0. His "satisfaction" will be greater in the case of rejection, and even generally increases as the observation that led to this rejection is significant. This is what users often highlight giving, at the end of the test procedure, the lowest value of the level p, it is the *p-value* for which the result ω''' obtained would be considered as significant.

2.2 Indices and prediction of satisfaction in the case of a study of two-stage test

Statisticians working for some application sectors such as clinical trials are more often faced with interlocutors who find too concise the categorical formulations that have been taught and which they have traditionally provided. For example, the use of classical test theory or confidence intervals is often felt by the practitioner as arbitrary and ill-suited to the preoccupations of experimental control.

Statistical practice mainly dominated by the use of tests is however an inevitable fact; but when planning experimental or intermediate analyzes and given the constraints which are legal and economic, tests are so onerous and there is often no interest to implement them if we can reasonably predict that they will lead to meaningful conclusions; hence the need for a first phase of preliminary testing lighter and less structured. We are therefore in a situation where the use of a classical test theory (Neymann-Pearson) is imposed. The dissymmetry "null hypothesis versus counter hypothesis" is implied by a stated desire to conclude in favor of the counter hypothesis. The user then wishes to be provided with a preliminary indication of the chances of seeing the realization of his desire, he is then mature to accept a Bayesian basis.

It is this context which has led some researchers to introduce statistical tools, called predictive. Our aim is to propose a systematization of this attitude, crossing the so-called classical statistics and Bayesian statistics or by considering a fully Bayesian approach and limiting ourselves to the case of tests.

For this purpose, we propose to the practitioner the use of indices that measure the degree of satisfaction with a given result or that reflect the prediction that he performs on a particular future event. These indicators occurring during or at the end of the experimental study are of a nature quite different from other assessment tools of a method such as the power function of a test. It is to be considered, in principle, prior the taking into account the experimental result which says little since the variable is the parameter, which remains unknown.
That is how, when the user practices a test, he does not simply say whether the result is significant at level α, but in this case likes to say to what value one could lower the level, *i.e.*, increase the severity of the test while keeping a significant result.

This practice is quite common, but is often content to be an indication "*en plus*". One of our intentions is to integrate it to the predictive approach outlined above.

- Presentation of prevision indices in the classical approach

α Being set, let a test of level α defined by the critical region $\Omega_1^{'''(\alpha)}$, a first index of satisfaction, the one studied in [11] is defined by:

$$\phi(\omega''') = 1_{\Omega_1^{'''(\alpha)}}(\omega''')$$

We propose a very interesting satisfaction index; one can consult in this respect [1, 2], considered as improved for its interest in the concept of predicting satisfaction and defined as a decreasing function of the conclusive measure p after the processing of the data in the following manner:

$$\phi(\omega''') = 0 \quad \text{if} \quad \omega''' \notin \Omega_1^{'''(\alpha)}$$
$$= 1 - \inf\left\{\beta;\ \omega''' \in \Omega_1^{'''(\beta)}\right\} \text{ if } \omega''' \in \Omega_1^{'''(\alpha)}$$

Other words:

$\phi(\omega''')=1 - p.$

In the logic of the introduction of the satisfaction index, it is natural to propose to characterize the value of the test procedure rather than by the power function, by a prevision index that is the mathematical expectation with respect to the predictive probability on the complete space conditioned by the result of the first phase. This concept is introduced when, as is often the case in clinical trials as in [13], where we must conduct a two-step experiment:

- A first result ω', determines whether or not we continue the experimentation,

- If the experimenter is highly satisfied and ones effectively continue the experimentation, then the resultω''' of the first and second phase is to base the test.

And if we denote $P_{\Omega'''}^{\omega'}$ the predictive probability on $\Omega'''=\Omega'\times\Omega''$ of ω''' conditionally on ω', we deduce a prevision index as:

$$\pi(\omega') = \int_{\Omega_1^{'''(\alpha)}} \phi(\omega''') P_{\Omega'''}^{\omega'}(d\omega''').$$

It is to the practitioner to decide below which value of the prevision of satisfaction; he gave up the pursuit of experience. Note that we use here both classical statistics and Bayesian statistics.
A standard situation is that where there exist an application $\Psi(\Theta\rightarrow\Re)$ such that:

$$\Theta_0 = \left\{\theta;\ \psi(\theta) \le t^*\right\}$$

and there are $(\Omega'''\rightarrow\Re)$ and $g(]0,1[\rightarrow\Re)$ such that:
$\Omega_1^{'''(\alpha)} = \left\{\omega'''; \xi(\omega''') \le g(\alpha)\right\}.$

Suppose further that the distribution of ξ under $P_{\Omega'''}^{\theta}$ depends only on $\psi(\theta)$ (we denote $Q_{\psi(\theta)}$) and that the family distributions Q_t is stochastically increasing, in the sense that ξ has a growing tendency to take large values when $\psi(\theta)$ becomes increasingly high.

Then, let G_t be the distribution function of Q_t. It is clear that:

$$\phi(\omega''') = 0 \quad \text{if} \quad \omega''' \notin \Omega_1^{'''(\alpha)}$$
$$= G_{t^*}(\omega''') \text{ if } \omega''' \in \Omega_1^{'''(\alpha)} \ ,$$

Where G_{t^*} is interpreted as the distribution function "at the frontier" of ξ. The prevision is then given by:

$$\pi(\omega') = \int_{\Omega_1^{'''(\alpha)}} \phi(\omega''') P_{\Omega'''}^{\omega'}(d\omega''')$$

$$= \int_{\Theta}\left[\int_{\Omega_1^{'''(\alpha)}} \phi(\omega''')\, P_{\Omega'''}^{\theta}(d\omega''')\right] P_{\Theta}^{\omega'}\, d\theta$$

$$= \int_{\Theta}\left[\int_{g(\alpha)}^{\infty} G_{t^*}(dx)\, dG_{\psi(\theta)}(x)\right] P_{\Theta}^{\omega'}(d\theta)$$

- Presentation of prevision indices in the Bayesian approach

A purely Bayesian point of view consists in choosing a probability μ, or more generally a σ-finished measure on Θ, and let $P_{\Theta}^{\omega'''}$ be the posterior probability on Θ, on the observation ω'''; it is conventional in Bayesian statistics to propose to treat the test situation of Θ_0 against Θ_1 by providing $P_{\Theta}^{\omega'''}(\Theta_1)$. It is indeed, clearly an index of satisfaction for those who want to conclude in favor of Θ_1, but without any reference to a level of precaution α.
If we denote $\widetilde{\Omega}_1^{'''(\alpha)}$ the rejection region of the Bayesian test at level α *i.e*,

$$\widetilde{\Omega}_1^{'''(\alpha)} = \{\omega'''; \ P_{\Theta}^{\omega'''}(\Theta_1) > 1 - \alpha\}.$$

Here again, a satisfaction index particularly interesting and better than the indicating function $\widetilde{\Omega}_1^{'''(\alpha)}$ is given by:

$$\widetilde{\phi}(\omega''') = 0 \quad \text{if} \quad \omega''' \notin \widetilde{\Omega}_1^{'''(\alpha)}$$
$$= P_{\Theta}^{\omega'''}(\Theta_1) \quad \text{if} \quad \omega''' \in \widetilde{\Omega}_1^{'''(\alpha)}$$

We have

$$\widetilde{\phi}(\omega''') \ge 1 - \alpha\,,$$

and we deduce the prediction:

$$\pi(\omega') = P_{\Omega'''}^{\omega'}\left(\widetilde{\Omega}_1^{'''(\alpha)}\right).$$

It is noticed that, in a very basic case such as *n*-independent real observations according to a one-dimensional normal distribution of unknown average θ and known variance where one tests the null hypothesis of the form $\theta \leq \theta_0$ and where one adopts a *non informative prior measure* in the sense of Jeffreys, *i.e.* here the Lebesgue measure, one well has in this case coincidence between the two approaches since:

$$\widetilde{\Omega}_1^{'''(\alpha)} = \Omega_1^{'''(\alpha)} \text{ and } \quad \widetilde{\phi} = \phi$$

3. APPLICATION TO THE GAUSSIAN MODEL

We propose to calculate the index and the prediction of satisfaction in the Gaussian model because of the centrality of this model in experimental sciences and especially for clinical trials when the prior distribution of the unknown parameter is a conjugate prior or a non informative.

The use of the conjugate distribution leads to relatively explicit formulas and to calculations of a reasonable complexity. This choice appears reasonable in practice and often when no information is available on the parameters, one can use Bayesian techniques that specify a state of ignorance. We will use the uninformative solution known as Jeffrey. One can consult in this respect [14].

3.1 Introduction of the model

Observations are made independent and of identical normal distribution $N(\theta, \sigma^2)$. In all what follows, Φ (*resp.* φ) denotes the cumulative distribution function (*resp. density*) of the distribution $N(0, 1)$.

The first result, $\underline{x}$ is a sequence $(x_1,....,x_k)$ for k observations and the second result, $\underline{y}$, is a sequence $(y_1,....,y_n)$. For obvious reasons of completeness, we will base all calculations on $x = \frac{1}{k}\sum_{i=1}^{k} x_i$ and $y = \frac{1}{n}\sum_{j=1}^{n} y_j$, of respective distributions $N(\theta, \sigma_1^2)$ and $N(\theta, \sigma_2^2)$, where

$$\sigma_1^2 = \frac{\sigma^2}{k} \text{ and } \sigma_2^2 = \frac{\sigma^2}{n}.$$

Here we assume σ^2 known and θ unknown.

3.2 Prediction for a prior conjugate distribution

We choose for the prior distribution for θ the natural conjugate, *i.e.*, here the normal distribution $\mu = N(\delta, \tau^2)$.

- Frequentist test. The frequentist test remains a difficult fact to get round in statistical methodology in clinical trials. It is proposed to explicitly and numerically calculate the index and prevision of satisfaction in the case of a test at level α, where the null hypothesis is of type $\theta \leq \theta_0$. We use a usual test on the results z of the first and second phase defined by:

$$z = \frac{kx + ny}{k + n}$$

Thus, the distribution of z is $N\left(\theta, \sigma_3^2\right)$ where

$$\sigma_3^2 = \frac{\sigma^2}{k + n}$$

The critical region of the test is $]q_0,+\infty[$ where $q_0 = \theta_0 + \sigma_3 u_\alpha^+$

And

$$\Phi\left(u_\alpha^+\right) = 1 - \alpha.$$

The satisfaction index is defined naturally as:

$$\phi(z) = \Phi\left(\frac{z - \theta_0}{\sigma_3}\right) \text{ if } z \geq q_0.$$
$$= 0 \quad \text{otherwise}$$

We know that the posterior distribution of θ after observing x is:

$$N\left(\frac{\tau^2 x + \sigma_1^2 \delta}{\sigma_1^2 + \tau^2}, \frac{\tau^2 \sigma_1^2}{\sigma_1^2 + \tau^2}\right)$$

and the predictive distribution of z/x is still a normal distribution $N(m', s'^2)$ where:

$$m' = \frac{kx}{k+n} + \frac{n}{k+n} \times \frac{\tau^2 x + \sigma_1^2 \delta}{\sigma_1^2 + \tau^2}$$

$$s'^2 = \frac{n^2}{(k+n)^2}\left(\sigma_2^2 + \frac{\tau^2 \sigma_1^2}{\sigma_1^2 + \tau^2}\right)$$

We can deduce the prediction by:

$$\pi(x) = \int_{q_0}^{+\infty} \Phi\left(\frac{z - \theta_0}{\sigma_3}\right) f^x(z)dz$$

In this particular case:

$$\pi(x) = \frac{1}{s'}\int_{q_0}^{+\infty} \Phi\left(\frac{z - \theta_0}{\sigma_3}\right)\varphi\left(\frac{z - m'}{s'}\right)dz$$

$$= \frac{1}{s'}\int_{\theta_0 + \sigma_3 u_\alpha^+}^{+\infty} \Phi\left(\frac{z - \theta_0}{\sigma_3}\right)\varphi\left(\frac{z - m'}{s'}\right)dz$$

$$t = \frac{z - m'}{s'} \quad \Rightarrow \quad z = ts' + m'$$

$$\pi(x) = \int_{\frac{\theta_0 + \sigma_3 u_\alpha^+ - m'}{s'}}^{+\infty} \Phi\left(\frac{ts' + m' - \theta_0}{\sigma_3}\right)\varphi(t)dt$$

$$= \int_{\frac{\theta_0 + \sigma_3 u_\alpha^+ - m'}{s'}}^{+\infty} \Phi\left(\frac{t + \frac{m' - \theta_0}{s'}}{\sigma_3 / s'}\right)\varphi(t)dt$$

$$\pi(x) = \left[1 - \Phi\left(\frac{\theta_0 + \sigma_3 u_\alpha^+ - m'}{s'}\right)\right]\int_R \Phi\left(\frac{t + \frac{m' - \theta_0}{s'}}{\sigma_3 / s'}\right)\frac{\varphi(t)}{1 - \Phi\left(\frac{\theta_0 + \sigma_3 u_\alpha^+ - m'}{s'}\right)} 1_{\left[\frac{\theta_0 + \sigma_3 u_\alpha^+ - m'}{s'}, \infty\right[}(t)dt$$

This integral is approximated by a Monte-Carlo method [15] by:

$$\left[1 - \Phi\left(\frac{\theta_0 + \sigma_3 u_\alpha^+ - m'}{s'}\right)\right]\left[\frac{1}{N}\sum_{i=1}^{n} \Phi\left(\frac{T_i + \frac{m' - \theta_0}{s'}}{\sigma_3 / s'}\right)\right],$$

where T_i are n realizations of the probability Q deduced from the standard normal distribution by the conditioning event

$$\left[\frac{\theta_0 + \sigma_3 u_\alpha^+ - m'}{s'}, \infty\right[$$

The draw of T_i runs as follows:
- U_i is drawn according to the uniform distribution $U_{[0,1]}$,

$$V_i = \left(\frac{\theta_0 + \sigma_3 u_\alpha^+ - m'}{s'}\right) + \left(1 - \Phi\left(\frac{\theta_0 + \sigma_3 u_\alpha^+ - m'}{s'}\right)\right)U_i,$$

in other words, V_i follows the uniform distribution on

$$\left[\frac{\theta_0 + \sigma_3 u_\alpha^+ - m'}{s'}, 1\right[,$$

$T_i = \Phi^{-1}(V_i)$,
We have T_i which follows the distribution Q.

A numerical application is considered below by simulations. As a result of these simulations, we obtain curves representing the prevision.

- Bayesian test. If the practitioner is considering a study in a fully Bayesian framework and uses a Bayesian type test based on the same prior $N(\delta, \tau^2)$ as the calculation of the prevision of satisfaction; the critical region of the Bayesian test is therefore:

$$\widetilde{\Omega}^{'''(\alpha)} = \{z;\ P_\Theta^z(\Theta_1) \geq 1 - \alpha\}.$$

The satisfaction index is given by:

$$\widetilde{\phi}(z) = 0 \quad \text{if} \quad z \notin \widetilde{\Omega}_1^{'''(\alpha)}$$
$$= P_\Theta^z(\Theta_1) \quad \text{if} \quad z \in \widetilde{\Omega}_1^{'''(\alpha)}$$

Recall that the posterior distribution of θ after having observed $\underline{z}$ is even a normal distribution $N(a_2, b_2^2)$ where:

$$a_2 = \frac{\tau^2 z + \sigma_3^2 \delta}{\sigma_3^2 + \tau^2}$$

and

$$b_2^2 = \frac{\sigma_3^2 \tau^2}{\sigma_3^2 + \tau^2}$$

If we set $\Phi(v_\alpha) = \alpha$, then the critical region is given by the set of elements z such that $z \geq Q_1$ with:

$$Q_1 = \frac{\theta_0(\sigma_3^2 + \tau^2) - v_\alpha \sigma_3 \tau \sqrt{\sigma_3^2 + \tau^2} - \sigma_3^2 \delta}{\tau^2}.$$

We deduce therefore the prediction of satisfaction index

$$\pi(x) = \int_{Q_1}^{\infty} \left(\int_{\theta_0}^{\infty} \frac{1}{b^2} e^{\left(\frac{\theta - a_2}{b_2}\right)^2} d\theta \right) f^x(z) dz,$$

where $f^x(z)$ is the density of the conditional predictive distribution of z given x which is none other than $N(m', s'^2)$ defined above.

The prediction can also be written as:

$$\pi(x) = \int_{Q_1}^{\infty} \Phi\left(\frac{a_2 - \theta_0}{b_2}\right) f^x(z) dz$$
$$= \int_{\frac{Q_1 - m'}{s'}}^{\infty} \Phi\left(\frac{z' - a''}{t''}\right) f^x(z') dz,$$

with

$$a'' = \frac{(\sigma_3^2 + \tau^2)\theta_0 - \tau^2 m' - \sigma_3^2 \delta}{\tau^2 s'}$$

and

$$t'' = \sigma_3 \tau (\sigma_3^2 + \tau^2)$$

Here again, there is no difficulty in approaching $\pi(x)$ by a Monte Carlo method. Note too, that the prediction has the same form as in the case of a classical test previously studied.

3.3 Prediction for a non-informative prior distribution

By adopting in this model a non-informative priors in the sense of Jeffrey, for example $\pi(\theta)=c$ (a constant), we know that the posterior distribution of θ after observing z is a normal distribution $N(z, \sigma_3^2)$ and the predictive distribution of z conditional on x is even a normal distribution:

$N(m'', s''^2)$

Figures 1 and 2 represent the prevision curves in the case of a frequentist test study, we chose N = 50, and graphs 3 and 4 represent the

with

$m'' = x$

and

$$s''^2 = \frac{n^2}{(k+n)^2}(\sigma_2^2 + \sigma_1^2)$$

We deduce that we really are in a borderline case of the previous study. The formalization is similar and the calculations are analogous and even simpler.

3.4 Presentation of numerical results

We wish to emphasize that the proposed predictive Bayesian approach can be used to predict results based on frequentist or Bayesian statements. We nevertheless believe that the frequentist approach provides a different insight on the data and should not be excluded. Prediction can be made as well for results derived from the frequentist approach as from the Bayesian approach. We present separately the numerical results to illustrate the achievement of original mathematical results with their pertinent application to the statistical analysis of real data. Prediction can be made as well for results derived from the frequentist approach as from the Bayesian approach.

The figures representing the prediction of satisfaction in terms of the observation x are presented below. *Simulation programs are written in MATLAB.*

In each graph, we took $\sigma^2 = 1$, $\delta = 0$ and $\tau = 1$ which does not diminish the generality. We also chose to plot the curves $\alpha = 0.01$, $\theta_0 = 0$ and $k = 10$. From one graph to the other varies the choice of σ_1^2, σ_2^2, σ_3^2, n and the type of the test, frequentist or Bayesian. The curves were plotted with a step of 0.01 for x and the following results are deduced for n = 10 or 20:

$n = 10$	$\sigma_1^2 = 0.1$	$\sigma_2^2 = 0.1$	$\sigma_3^2 = 0.05$
$n = 20$	$\sigma_1^2 = 0.1$	$\sigma_2^2 = 0.05$	$\sigma_3^2 = 0.0333$

prevision curves in the case of a Bayesian test study. Recall that in this case our study is fully Bayesian and requires a larger number of simulations.

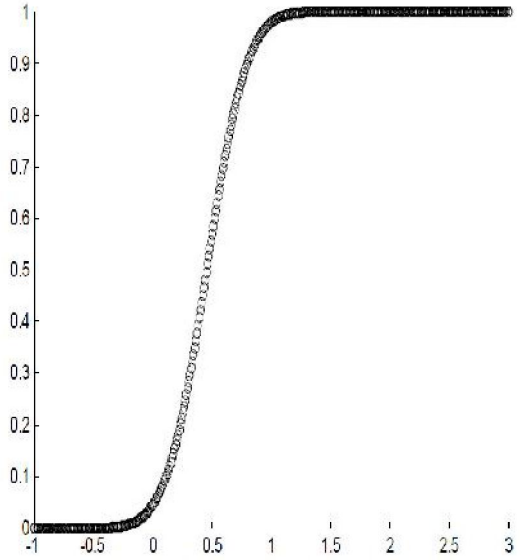

Figure 1. Prediction of satisfaction in a frequentist test case where $\alpha = 0.01$, $k = 10$, $n = 20$.

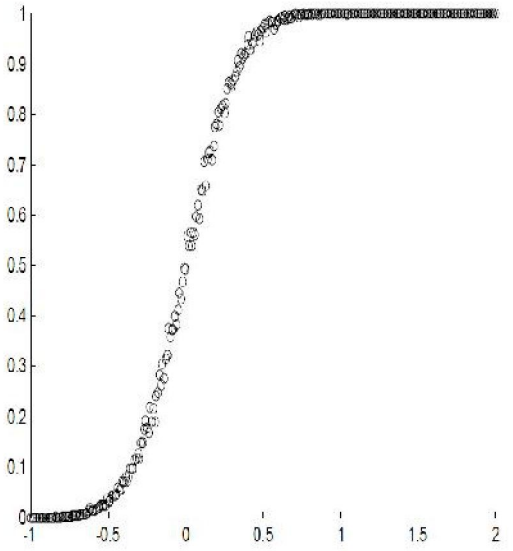

Figure 3. Prediction of satisfaction in a Bayesian test case where $\alpha = 0.01$, $k = 10$, $n = 20$.

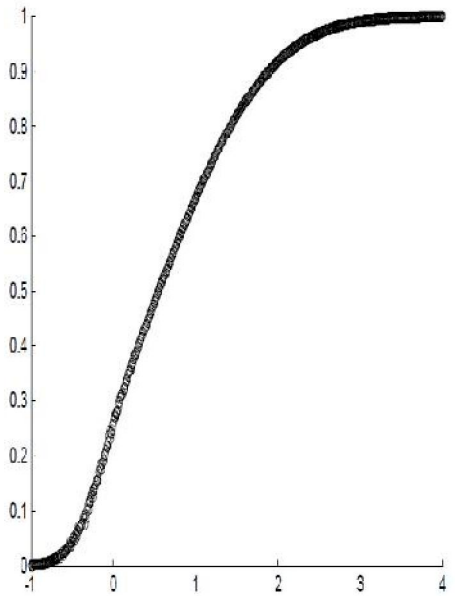

Figure 2. Prediction of satisfaction in a frequentist test case where $\alpha = 0.01$, $k = 10$, $n = 10$.

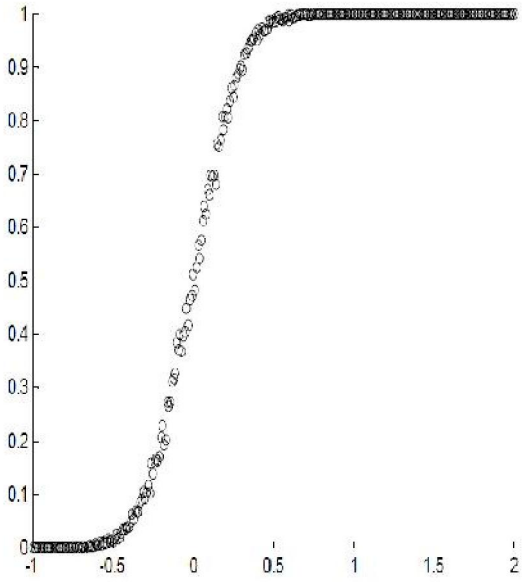

Figure 4. Prediction of satisfaction in a Bayesian test case where $\alpha = 0.01$, $k = 10$, $n = 10$.

Note that:

Frequentist test for $x = 0.5$ and $N = 50$:

k =10	$n = 20$	$\pi(0.5) = 0.454$
$k = 10$	$n = 10$	$\pi(0.5) = 0.481$

Bayesian test for $x = 0.5$ and $N = 50$:

$k = 10$	$n = 20$	$\pi(0.5) = 0.926$
$k = 10$	$n = 10$	$\pi(0.5) = 0.963$

The predictive approach therefore applies equally to the conclusions drawn from frequentist procedures as Bayesian. Even if our point of view is to focus on fully Bayesian methodology for analysis of experimental trials, we believe that the frequentist practice is now *a de facto* essential in the experimental context.

The predictive Bayesian approach allows to take or not to take into account the contribution of the information outside the test under study.

4. CONCLUSION

The predictive procedures provide solutions to make a decision to stop the experiment before its term. It is explicitly interesting since they allow for ethical reasons particularly in clinical trials in humans involving patients' survival to expose the least possible subject to the least effective therapy. The predictive probability of obtaining the desired conclusion is an important element to consider in the decision. A probability very high or very low is an argument in favor of the termination of the test. We defined an index that meets the requirements of adequacy (through the inclusion of the *p-value*) and simplicity in calculations.

We subsequently have proposed a prediction that relates to the whole data, those available as well as future data. In order to satisfy the users of statistical tests for the statistical analysis of real data, we have procedures mixtures of frequentist and Bayesian procedures. This crossing was possible because of the particular nature of clinical trials taking place in accordance with the legal instructions in two stages, the first used to determine the merits to proceed with the second.

We also considered here solutions in a fully Bayesian framework and the corresponding calculations of prediction is feasible by Monte Carlo methods. The numerical applications and simulation results in the Gaussian model illustrate the innovative methodology and provide the practitioner with tools ready to use.

In brief, this is an extremely useful work for clinical trials statisticians wishing to stay abreast with the innovative approaches that are being developed amid some controversies regarding their benefits. We think it provides a valuable contribution to the area of design of sequential clinical trials.

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