CHOICE OF THE PRIOR IN THE BAYESIAN DESIGN FOR THE CLINICAL TRIALS.

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Abstract

Bayesian statistics have the advantage of being easily established and derived. Thus, we will use this approach to find the distribution of the predictive probabilities of the data not observed yet in the conception of clinical trials phase II. Such perspectives are necessary in cases or in reason treat ethical preoccupations or ether to achieve trials which are particularly toxic or expensive. We propose, in reason of neutrality, to calculate the predictive probabilities within a Bayesian case, where the prior is non informative in different models apply in clinical trials.

Keywords: *Bayesian prediction, p-value, clinical trials, non informative prior.*

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I- Introduction

Clinical trials are prospective studies to evaluate the effect of interventions in humans under prespecified conditions. They have become a standard and integral part of modern medicine. A properly planned and executed clinical trial is the most definitive tool for evaluating the effect and applicability of new treatment modalities ([3]; [4]; [5]; [7]). The methodology adapted to the context of clinical trials is characterized by many constraints and unsatisfactions and form the subject of a deep and continuous development ([1]; [5]; [6]; [8). One of the reasons of such interest likely holds from the fact that public health authorities are responsible for the authorization of putting the drugs into market and they play a primordial role in the elaboration of rigorous methodology of clinical trials in the view of all the actors in this field (industries, public institutes of research, hospitals and scientific journals).

The clinical trials primary goal is to evaluate the efficiency and the tolerance of a new medical treatment, they are characterized by complex actions that can't be readily modeled and they do not depend solely on statistical considerations (see for example Shein-Chung Chow, and al., [2]).

The Bayesian approach brings a major flexibility to the statistic methodology of the clinical trials. In particular we are interested to use this approach in prediction in the context of clinical trials because of the critical role which play the predictive probability in the design of a trial and also in monitoring trials. In this situation, often we have got primary experimental information in the form of phase I which we need to confirm some results ([2], [8]). Formally, we consider the following situation: To go by the data of the first sample, we can plan an experience (a new sample) so as to have good chances to get the intended conclusion if the experimentation is not discarded. We propose the procedure based on the concept of the index of satisfaction which is a function of the *p-value*, and we envisage, given the available data, to calculate a predicted satisfaction of this index conditioning to the previous observations ([8]). To illustrate this procedure, we will study several exponential models chosen a non-informative prior to make evidence to the analysis objectivity of the experimental data. The numeric calculations and the simulation results are presented in the form of Gaussian model.

2. Statistic method :

We recall (see Merabet [8]), that the experimental context consists of two successive experimentations, of results $\omega' \in \Omega'$ and $\omega'' \in \Omega''$, which are in general carried out independently. Their distributions built in the framework of a well established model, depend on a parameter $\theta \in \Theta$, only $\omega"$ is used to found the official conclusion of the study and to determine the user satisfaction denoted $\phi(\omega")$ (and on the choice about which we will come back in 3). But, on the basis of the result ω' of first step clinical trial, it is useful to anticipate what the satisfaction will be well after the second step. In our study, this prediction is carried out in a bayesian context, i.e., based on the choice of a prior probability on Θ. We therefore define the indicator of prediction as:

$$\pi(\omega') = \int_{\Omega''} \phi(\omega") P_{\Omega''}^{\omega'}(\omega'') \qquad (1)$$

Where $P_{\Omega''}^{\omega'}(\omega'')$ is the probability on Ω'', conditioned by the result of the first step, and $\phi(\omega")$ is the index of satisfaction, given also as:

$$\pi(\omega') = \int_{\theta} \left(\int_{\Omega''} \phi(\omega") P_{\Omega''}^{\theta}(\omega'') \right) P_{\theta}^{\omega'}(\theta) \qquad (2)$$

Were $P^{\theta}_{\Omega''}(\omega'')$ is the sampling distribution of the second step, and $P^{\omega'}_{\Theta}(\theta)$ is the posterior probability on Θ, based on the result of the first step. Let us consider the case where one has densities relative with measurements μ, ν' and ν'' on Θ, Ω' and Ω'', that of the prior P_Θ being denoted g and those of the sampling probabilities $P^{\theta}_{\Omega'}$ and $P^{\theta}_{\Omega''}$ being denoted $f'(.|\theta)$ and $f''(.|\theta)$ respectively. (1) and (2) then become:

$$\pi(\omega') \frac{\int_{\Omega''} \phi(\omega'') \left(\int_{\Theta} f'(\omega'|\theta) f''(\omega''|\theta) g(\theta) \mu(d\theta) \right) \nu''(d\omega'')}{\int_{\Theta} f'(\omega'|\theta) g(\theta)\, \mu(d\theta)} \quad (3)$$

And

$$\pi(\omega') = \frac{\int_{\Theta} \left(\int_{\Omega''} \phi(\omega'') f''(\omega''|\theta) \nu''(d\omega'') \right) f'(\omega'|\theta) g(\theta) \mu(d\theta)}{\int_{\Theta} f'(\omega'|\theta) g(\theta)\, \mu(d\theta)} \quad (4)$$

2.1. Index of satisfaction

This concept is important when the statistician, who carries out a test, "wishes" to observe a significant result, that is to reject the null hypothesis H_0. Its satisfaction will be thus larger in the event of rejection, and even in general as much larger as the observation that leads to this rejection is more significant. It's what even the users put in an obvious place, at the end of a test, not only the conclusion "all or nothing" (significant or not significant) but also the smaller value of threshold for which the result $\underline{y}$ observed will be considered significant that is in theory of the test, the *p-value*.

Being α fixed let a test of level α be defined by a critical region $\Omega_1^{''(\alpha)}$. It is more interesting to take into account to what level will be the results always appear significant. We will use a new index of satisfaction, that was study by Merabet H. (2004), and defined for the Bayesian tests, based on the same prior P_Θ, as:

$$\phi(\omega'') = \begin{cases} 0 & if \quad \omega'' \in \Omega_0^{''(\alpha)} \\ 1 - inf\left\{\beta; \omega'' \in \Omega_1^{''(\beta)}\right\} & if \quad \omega'' \in \Omega_1^{''(\alpha)} \end{cases}$$

(5)

A standard situation is that where it exists an application $\psi(\Theta \to \mathbb{R})$ such as $\Theta_0 = \{\theta;\ \psi(\theta) \le t_0\}$ and where it also exists $\xi(\Omega'' \to \mathbb{R})$ and $g(]0,1[\to \mathbb{R})$ such that

$$\Omega_1^{''(\alpha)} = \{\omega'';\ \xi(\omega'') \le g(\alpha)\}$$

Where $g(\alpha)$ is the $(1-\alpha)$ fractile of the distribution of ξ when $\psi(\theta_0) = t_0$. It thus appears natural to use the p-value to define the satisfaction indexes that are null if a significant effect is not detected, and in the opposite case are an increasing function of the classical indicator of significance. In this case

$$p(\omega'') = P_{\theta_0}\left(\xi > \xi(\omega'')\right)$$

An index of satisfaction is thus defined naturally as:

$$\phi(\omega'') = \begin{cases} 0 & if \quad \xi(\omega'') \le g(\alpha) \\ L\left(p(\omega'')\right) & if \quad \xi(\omega'') > g(\alpha) \end{cases} \quad (6)$$

Where L is a decreasing function. Let F_{θ_0} be a distribution of ξ at the frontier, i. e., for any θ_0 such as $\psi(\theta_0) = t_0$, the index of satisfaction is defined by:

$$\phi(\omega'') = \begin{cases} 0 & if \quad p(\omega'') \ge 1-\alpha \\ L\left(1 - F_{\theta_0}(\omega'')\right) & else \end{cases} \quad (7)$$

The prediction is then given by:

$$\pi(\omega') = \int_{\{\omega'';\, \xi(\omega'') > g(\alpha)\}} L\left(1 - F_{\theta_0}(\omega'')\right) P^{\omega'}_{\Omega''}(\omega'') \quad (8)$$

3. Application :

We propose to calculate explicitly or numerically the prediction of satisfaction in several exponential models for $L(p) = (1-p)$ when the prior distribution of the unknown parameter θ is non-informative (see Robert, 2006) and in the case of a test of threshold, α where the null hypothesis is of type $\theta \le \theta_0$.

3.1. Poisson Sampling :

Let us suppose that X'_i $(1 \le i \le n)$ and X''_i $(1 \le i \le k)$ are *i.i.d.* normal random variables of Poisson distribution $\mathcal{P}(\theta)$, where θ is unknown.
Then $\omega' = \sum_{i=1}^{n} X'_i$ have a Poison distribution $\mathcal{P}(n\theta)$ and $\omega'' = \sum_{i=1}^{k} X''_i$ have a Poisson distribution $B(k\theta)$. If θ has a non informative prior

$$f(\theta) = \theta^{-1}$$

Then the posterior density of θ given ω' will be

$$f(\theta|\omega') \propto Gamma(\omega', n)$$

And the predictive of ω'' given ω' is

$$\nu(\omega''|\omega') = \frac{\Gamma(\omega' + \omega'')}{\Gamma(\omega')\omega''!} \left(\frac{n}{n+k}\right)^{\omega'} \left(\frac{k}{n+k}\right)^{\omega''}$$

The index of satisfaction is then expressed as:

$$\phi(\omega'') = \begin{cases} 0 & if \quad \omega'' < q_0 \\ \sum_{s=0}^{\omega''-1} e^{-k\theta_0} \frac{(k\theta_0)}{s!} & if \quad \omega'' \ge q_0 \end{cases}$$

Where

$$q_0 = inf\left\{s; \sum_{s=0}^{u-1} e^{-k\theta_0} \frac{(k\theta_0)}{s!} \ge 1-\alpha\right\}$$

And the prediction of satisfaction is given by:

$$\pi(\omega') = \sum_{\omega''=q_0}^{\infty} \left(\sum_{s=0}^{\omega''-1} e^{-k\theta_0} \frac{(k\theta_0)}{s!} \right) \nu(\omega''|\omega')$$

$$= \sum_{\omega''=q_0}^{\infty} \left(\sum_{s=0}^{\omega''-1} e^{-k\theta_0} \frac{(k\theta_0)}{s!} \right) \frac{\Gamma(\omega'+\omega'')}{\Gamma(\omega')\omega''!} \left(\frac{n}{n+k}\right)^{\omega'} \left(\frac{k}{n+k}\right)^{\omega''}$$

3.2.Gamma distribution

Let us suppose that X'_i $(1 \le i \le k)$ and X''_i $(1 \le i \le n)$ are *i.i.d.* normal random variables of Gamma distribution $G(p,\theta)$ where θ is unknown and p is known. Then, $\omega' = \sum_{i=1}^{k} X'_i$ have a Gamma distribution $G(kp,\theta)$ and $\omega'' = \sum_{i=1}^{n} X''_i$ have a Gamma distribution$B(np,\theta)$. Let be $K = kp$ and $N = np$.
If θ has a non informative prior $f(\theta) = \theta^{-1}$. Then the posterior density of θ given ω' will be:

$$f(\theta|\omega') \propto Gamma(K,\omega')$$

And the predictive of ω'' given ω' is:

$$\nu(\omega''|\omega') = \frac{1}{\beta(N,K)} \frac{(\omega'')^{N-1}(\omega')^{K}}{(\omega''+\omega')^{N+K}}$$

The index of satisfaction is then expressed as:

$$\phi(\omega'') = \begin{cases} 0 & if \quad \omega'' < q_0 \\ F(\omega'') = \int_0^{\omega''} \frac{(\theta_0)^N}{\Gamma(N)} t^{N-1} e^{-t\theta_0} dt & if \quad \omega'' \ge q_0 \end{cases}$$

Where $F(q_0) = 1-\alpha$.
And the prediction of satisfaction is given by:

$$\pi(\omega') = \int_{q_0}^{\infty} \left(\int_0^{\omega''} \frac{(\theta_0)^N}{\Gamma(N)} t^{N-1} e^{-t\theta_0} dt \right) \nu(\omega''|\omega') \mathrm{d}\omega''$$

$$= \int_{q_0}^{\infty} \left(\int_0^{\omega''} \frac{(\theta_0)^N}{\Gamma(N)} t^{N-1} e^{-t\theta_0} dt \right) \frac{1}{\beta(N,K)} \frac{(\omega'')^{N-1}(\omega')^{K}}{(\omega''+\omega')^{N+K}} \mathrm{d}\omega''$$

This can be estimated numerically.

3.3. Gaussian model

- We will interest ourselves with the Gaussian model because of its central character in experimental sciences and in particular for the clinical trials. The corresponding calculations of the prevision can be realizable by the Monte-Carlo methods.
- We perform independent observations of same normal random variable $\mathcal{N}(\theta,\sigma^2)$. In all that follows, Φ andφ (resp. T_{n-1} and t_{n-1}) indicates the cumulative distribution function and the density of the distribution $\mathcal{N}(0,1)$ respectively (resp. of the student distribution $\mathcal{T}_1(n-1,0,1)$) .
- The first result; $\underline{x} = (x_1, x_2, \dots, x_n)$, is a series of n observations and the second result is a series; $\underline{y} = (y_1, y_2, \dots, y_k)$.
- For obvious reasons of exhaustiveness we will base all calculations on $x = \frac{1}{n}\sum_{i=1}^{n} x_i$ and $y = \frac{1}{k}\sum_{j=1}^{k} y_j$, of distributions $\mathcal{N}(\theta,{\sigma_1}^2)$ and $\mathcal{N}(\theta,{\sigma_2}^2)$, respectively, where ${\sigma_1}^2 = \frac{\sigma^2}{n}$ and ${\sigma_2}^2 = \frac{\sigma^2}{k}$.
- We suppose here that σ^2 is unknown (so ${\sigma_1}^2$ and ${\sigma_2}^2$). We choose as a priori distribution for (θ,σ^2) the non-informative distribution $\pi(\theta,\sigma^2) = \frac{1}{\sigma}$ (See Robert, 2006). We wish to test a null assumption of type $\theta \le \theta_0$.
- We use here a usual test ranging on $\underline{y}$, whose critical region is $]q_0, +\infty[$, where $q_0 = \theta_0 + \sigma_2 u_\alpha^+$, u_α^+ indicating the upper α quartile of the standard normal distribution $\mathcal{N}(0,1)$: $\Phi(u_\alpha^+) = 1-\alpha$.The posterior density associated to the prior $\pi(\theta,\sigma^2) = \frac{1}{\sigma}$ and applied to the second phase $\underline{y} = (y_1, y_2, \dots, y_k)$ is then:

$$\theta \left| \sigma, y, {S_2}^2 \sim \mathcal{N}\left(y, \frac{\sigma^2}{k}\right) \right. and \ \sigma^2 \left| y, {S_2}^2 \sim \mathcal{IG}\left(\frac{k-1}{2}, \frac{{S_2}^2}{2}\right)\right.$$

Where $y = \frac{1}{k}\sum_{j=1}^{k} y_j$ and ${S_2}^2 = \frac{1}{k}\sum_{j=1}^{k}(y_j - y)^2$. And the predictive density of y given x is given by:

$$f_x(y) = \frac{\Gamma\left(\frac{n}{2}\right)}{\sqrt{\pi}\Gamma\left(\frac{n-1}{2}\right)} \frac{1}{\frac{S_1}{\sqrt{\frac{nk}{n+k}}}} \left(\frac{(y-x)^2}{\frac{S_1^2}{\frac{kn}{(n+k)}}} + 1 \right)^{-\frac{n}{2}}$$

Where ${S_1}^2 = \frac{1}{n}\sum_{i=1}^{n}(x_i - x)^2$.

We identify a student distribution $\mathcal{T}_1\left(n-1, x, \frac{S_1}{\sqrt{\frac{nk}{n+k}}}\right)$.

Finally the prevision of satisfaction is:

$$\pi(x) = \int_{q_0}^{+\infty} \Phi\left(\frac{y-\theta_0}{\frac{S_2}{\sqrt{k}}}\right) \times \frac{\Gamma\left(\frac{n}{2}\right)}{\sqrt{\pi}\Gamma\left(\frac{n-1}{2}\right)} \frac{1}{\frac{S_1}{\sqrt{\frac{nk}{n+k}}}} \left(\frac{(y-x)^2}{\frac{S_1^2}{\frac{kn}{(n+k)}}} + 1 \right)^{-\frac{n}{2}} dy$$

3.3.1. Monte Carlo's Method

In order to carry out the calculation of $\pi(x)$ using a Monte Carlo method, and by change of variable, we rewrite it in the following form:

$$\pi(x) = [1 - T_{n-1}(a + \gamma u_\alpha^+)] \int_{-\infty}^{+\infty} \Phi\left(\frac{z - a}{\gamma}\right) \times \frac{t_{n-1}(z)}{1 - T_{n-1}(a + \gamma u_\alpha^+)} \mathbb{I}_{[a+\gamma u_\alpha^+, +\infty[} dz$$

Where $a = \frac{\sqrt{n-1}}{S'_1}(\theta_0 - x)$, $\gamma = \sqrt{n-1}\frac{S'_2}{S'_1}$ with $S'_1 = \frac{S_1}{\sqrt{\frac{nk}{n+k}}}$, $S'_2 = \frac{S_2}{\sqrt{k}}$ and $\frac{t_{n-1}(z)}{1-T_{n-1}(a+\gamma u_\alpha^+)} \mathbb{I}_{[a+\gamma u_\alpha^+, +\infty[}$ is the probability density Q deduced from the cumulative distribution function of the student distribution by conditioning by the event $[a + \gamma u_\alpha^+, +\infty[$.
The Monte Carlo method then consists in approaching $\pi(x)$by:

$$[1 - T_{n-1}(a + \gamma u_\alpha^+)] \left[\frac{1}{N}\sum_{i=1}^{N} \Phi\left(\frac{Z_i - a}{\gamma}\right)\right]$$

Where the Z_i are N realisations of the probability Q. The pulling of the Z_i proceeds in the following way:

- U_i is drawn according to the uniform distribution on$[0,1]$.
- $V_i = T_{n-1}(a + \gamma u_\alpha^+) + \left(1 - T_{n-1}(a + \gamma u_\alpha^+)\right)U_i$; *i.e.,* that V_i follows the uniform distribution on $[T_{n-1}(a + \gamma u_\alpha^+), 1]$.
- $Z_i = {T^{-1}}_{n-1}(V_i)$, i.e., that Z_i follows the distribution Q.

3.3.2. Result's representation :

One will find below the representative curves of π as a function of the number of Monte Carlo samples. We have considered only the case $\theta_0 = 0$ and in the first as in the second sample, the observations are of the same unit variance $\sigma^2 = 1$, considering that a modification of θ_0 and σ^2 will only result in a translation. We have considered the two cases: when $\alpha = 0.05\ and\ \alpha = 0.01$. In other hand, we have taken $k = 30$ and $n = 40\ or\ n = 50$.

- The graphs (1- 2) represent the prevision of satisfaction when $\alpha = 0.05$. The first one is for $n = 40$ and the second is for $n = 50$. We see clearly that the satisfaction augment with n.
- The graphs (3- 4) represent the prevision of satisfaction when $\alpha = 0.05$, also for $n = 40\ and\ n = 50$ respectively. We observe the same remark but the values are reduced.
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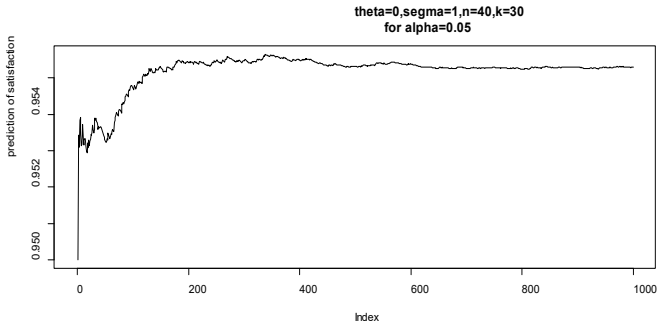

Fig. 1: Convergence of a Monte Carlo sequence for the predictive index of satisfaction based on 1000 iterations, for $\alpha = 0.05\ and\ n = 40$.

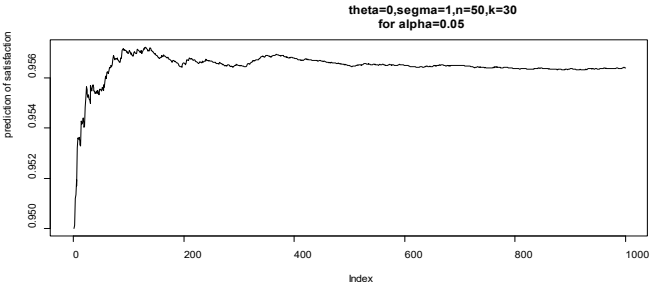

Fig. 2: Convergence of a Monte Carlo sequence for the predictive index of satisfaction based on 1000 iterations for $\alpha = 0.05\ and\ n = 50$.

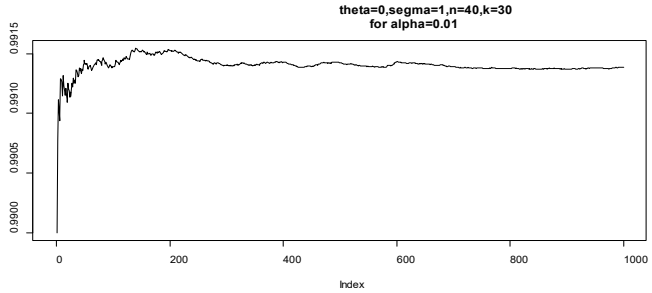

Fig. 3: Convergence of a Monte Carlo sequence for the predictive index of satisfaction based on 1000 iterations for $\alpha = 0.01\ and\ n = 40$.

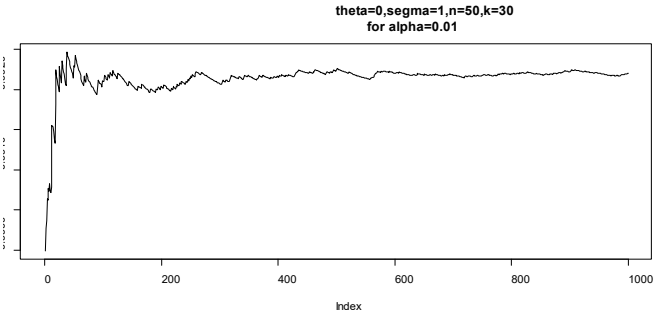

Fig. 4: Convergence of a Monte Carlo sequence for the predictive index of satisfaction based on 1000 iterations $\alpha = 0.01\ and\ n = 50$.

CONCLUSION

The main object of this paper is to chow the important role of the Bayesian predictive procedure applied to a family of limited indices of satisfaction introduced by H. Merbet (2004) which was the generalization of the "rudimentary" index of satisfaction considered by Grouin (1994).

The methodology is useful in two-steps testing procedures, such as those considered in the clinical trials context. The result of the first step is used to decide if the experiment will be continued. Given the posterior distribution derived from the available data, the prevision of satisfaction is defined like the predictive expectation of the index of

satisfaction for the future sample (the interpretation of the index being left to the expert). We consider different cases of the application of the proposed procedure with a non-informative prior.

Bayesian clinical trial simulation is a generic tool that can compute the predictive satisfaction for any trial result, whether that is based on a Bayesian analysis of the data, frequentist significance tests or a formal decision analysis such as a decision by a health care provider to put a drug in the market. In our paper, we have taken an inferential problem related to the Gaussian model.

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