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# INDEX AND PREVISION OF SATISFACTION IN EXPONENTIAL MODELS FOR CLINICAL TRIALS

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## 1. INTRODUCTION

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. 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 a rigorous methodology of clinical trials in the view of all the actors in this field (industries, public institutes of research, hospitals, scientific journals). The clinical trials primary goal is to evaluate the efficacy and the tolerance of a new medical treatment, they are characterized by complex actions that can not be readily modeled and they do not depend solely on statistical considerations (see for example (Holst *et al.*, 2001)). Moreover, statisticians working for certain application sectors, such as clinical trials find themselves more and more faced with interlocutors who find too basic the distinct formulations that were taught and traditionally supplied to them. For example, the use of the classical theory of trials or of intervals of trust is often felt by the practitioner as arbitrary and badly adapted to the preoccupations of experimental testing. One can refer in this to (Grieve, 1992; Grouin, 1994; Merabet and Raoult, 1995). It is this context that have led to the introduction of statistical tools known as predictive. To that effect, we propose to the practitioner the use of indexes that measure its degree of satisfaction in the face of such or such result or that express the prediction that he undergoes on such or such future event.

## 2. EXPERIMENTAL MODEL

We recall (see Merabet and Raoult, 1995), 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 $\omega'$ of first step clinical trial, it is useful to anticipate what the satisfaction will be well after the second step. In our study, as discussed in Grouin (1994), this prevision is carried out in a Bayesian context, *i.e.*, based on the choice of a prior probability on $\Theta$.

We denote:

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

$P_\Theta$: Prior probability on $\Theta$,

$P_\Theta^{\omega'}$ : Posterior probability on $\Theta$, based on the result of the first step,

$P_{\Omega''}^{\theta}$ : Sampling distribution of the second step,

$P_{\Omega''}^{\omega'}$ : Probability on $\Omega''$, conditioned by the result of the first step $\omega'$.

What interests the potential user of the indicator of satisfaction $\phi(\omega'')$, is, well after the first step clinical trial, the prevision of its average value knowing $\omega'$.

We therefore define the indicator of prediction as:

$$\pi(\omega') = \int_{\Omega''} \phi(\omega'')\, P_{\Omega'}^{\omega'}\ (d\omega'') \tag{1}$$

Where $\phi(\omega'')$ is the indicator of satisfaction, given also as:

$$\pi(\omega') = \int_{\Theta} \left( \int_{\Omega'} \phi(\omega'')\ P_{\Omega''}^{\theta}\ \ (d\omega'') \right) P_{\Theta}^{\omega'}\ (d\theta) \tag{2}$$

Let us consider the case where one has densities relative with measurements $\mu$, $\nu'$ and $\nu''$ on $\Theta$, $\Omega'$ and $\Omega''$, that of the prior $P_\Theta$ being denoted $g$ and those of the sampling probabilities $P_{\Omega'}^{\theta}$ and $P_{\Omega''}^{\theta}$ being denoted $f\,'(./\theta)$ and $f\,''(./\theta)$, respectively.

(1) and (2) then become:

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

and

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

## 3. INDEX OF SATISFACTION

We will place ourselves within the framework where the statistician "wishes" to observe a significant result, that is, to reject the null hypothesis $\Theta_0$. 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.

### 3.1. *Rudimentary index*

Being $\alpha$ fixed, let a test of level $\alpha$ be defined by a critical region $\Omega_1^{''(\alpha)}$. A first index of satisfaction (that studied by Grouin (1994)) is defined by:

$$\phi(\omega'') = 1_{\Omega_1^{''(\alpha)}}(\omega''); \tag{5}$$

at fixed $\omega'$, the prevision is then

$$\pi(\omega') = P_{\Omega''}^{\omega'}(\Omega''^{(\alpha)}_1) = \int_{\Theta} P_{\Omega''}^{\theta}(\Omega_1^{''(\alpha)}) P_{\Theta}^{\omega'}(d\theta), \tag{6}$$

where $P_{\Omega'}^{\theta}(\Omega_1^{''(\alpha)})$ is the value in $\theta$ of the power of the test.

### 3.2. *Improved index*

The default of the above rudimentary index is that it expresses a satisfaction in "all or nothing". It is more interesting to take into account to what level will the result always appears significant. One thus uses a new index of satisfaction defined by:

$$\begin{aligned}\phi(\omega'') &= 0 \ \text{ if } \ \omega'' \in \Omega_0^{''(\alpha)} \\ &= 1 - \inf\{\beta;\ \omega \in \Omega_1^{''(\beta)}\} \ \text{ if } \ \omega'' \in \Omega_1^{''(\alpha)}\end{aligned} \tag{7}$$

and obviously the prediction is given by:

$$\begin{aligned}\pi(\omega') &= \int_{\Omega_1^{''(\alpha)}} \phi(\omega'')\, P_{\Omega''}^{\omega'}(d\omega'') \\ &= \int_{\Theta} \left( \int_{\Omega_1^{''(\alpha)}} \phi(\omega'')\, P_{\Omega''}^{\theta}(d\omega'') \right) P_{\Theta}^{\omega'}(d\theta').\end{aligned} \tag{8}$$

It is noticed that $\int_{\Omega_1^{''(\alpha)}} \phi(\omega'')\, P_{\Omega''}^{\theta}(d\omega'')$ generalizes the power of the test in the logic of the index of satisfaction proposed.

A standard situation is that where it exists an application $\psi(\Theta \to \Re)$ such as $\Theta_0 = \{\theta; \psi(\theta) \le t_0\}$ and where it also exists $\xi(\Omega'' \to \Re)$ and an application $g(]0,1[ \to \Re)$ such as $\Omega_0^{''(\alpha)} = \{\omega''; \xi(\omega'') \le g(\alpha)\}$.

We assume moreover that the distribution of $\xi$ under $P_{\Omega''}^{\theta}$ depends only on $\psi(\theta)$ (it is denoted $Q_{\psi(\theta)}$) and is stochastically increasing, in the way where $\xi$ tends more and more to take great values when $\psi(\theta)$ becomes increasingly large.

A test, with threshold $\alpha$ of $\Theta_0$ is then naturally defined by rejecting the assumption if the experimental result, is $\omega''$, verifies $\xi(\omega'')>g(\alpha)$ where $g(\alpha)$ is the (1-$\alpha$) fractile of the distribution of $\xi$ when $\psi(\theta_0)=t_0$.

It thus appears natural to consider 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 that is in theory of tests, the $p$-value.

In this case:

$$p(\omega'') = P_{\theta_0}(\xi > \xi(\omega'')) . \tag{9}$$

An index of satisfaction is thus defined naturally as

$$\begin{aligned} \phi(\omega'') &= 0 \quad \text{if } \xi(\omega'') \le g(\alpha) \\ &= L(p(\omega'')) \quad \text{if } \xi(\omega'') > g(\alpha) \end{aligned} \tag{10}$$

where $L$ is a decreasing function.

Or if one notes $F_{\theta_0}$ the distribution of $\xi$ at the frontier, *i.e.*, for any $\theta_0$ such as $\psi(\theta_0)=t_0$, the index of satisfaction is defined by

$$\begin{aligned} \phi(\omega'') &= 0 \quad \text{if } p(\omega'') \ge 1-\alpha \\ &= L(1-F_{\theta_0}(\omega'')) \text{ else.} \end{aligned} \tag{11}$$

The prevision is then given by

$$\pi(\omega') = \int_{\{\omega'';\ \xi(\omega'')\ >\ g(\alpha)\}} L(1-F_{\theta_0}(\xi(\omega''))) \, P_{\Omega''}^{\omega'}(d\omega'') . \tag{12}$$

We can generalize this procedure to a family of limited indices defined by: $L(p) = (1-p)^l$ where $l \ge 0$. It is preferable to choose limited indexes because of their easier interpretation.

In the case where $l=1$, 1-$\phi(\omega'')$ is the $p$-value and in the case where $l=0$, one finds the indicator function of the critical region.

## 4. APPLICATIONS

One proposes to calculate explicitly or numerically, according to the case, the index and the prevision of satisfaction in several exponential models for $l=1$, when the prior distribution of the unknown parameter $\theta$ is a conjugate prior (Robert, 1992) and in the case of a test of threshold, $\alpha$, where the null hypothesis is of type $\theta \le \theta_0$.

We perform independent observations and of same distribution. The first result is a series $X_1'$, ..., $X_k'$ of $k$ observations and the second is also a series

$X_1''$, ..., $X_n''$ of *n* observations. All the calculations are, for reasons of exhaustiveness, based on $\sum_{i=1}^{k} X_i'$ and $\sum_{i=1}^{n} X_i''$ .

In all what follows, one explicitly calculates the index and the prevision of satisfaction and these are the following simplified notations:

*g*: density of the prior distribution of $\theta$,

*l*: density distribution of the couple ($\omega'$, $\omega''$),

*v*: conditional predictive distribution density of $\omega''$ given $\omega'$,

*F*: cumulative distribution function of the distribution of $\omega''$ for the value $\theta_0$ of the parameter.

4.1. *Gamma distribution*

Let us suppose that $X_i'(1 \le i \le k)$ and $X_j''(1 \le j \le n)$ are *i.i.d.* normal random variables of Gamma distribution $G(p, \theta)$ where $\theta$ is unknown and *p* is known. Then, $\omega' = \sum_{i=1}^{k} X_i'$ and $\omega'' = \sum_{i=1}^{n} X_i''$ are the Gamma distributions $G(kp,\theta)$ and $G(np, \theta)$, respectively.

Let be $kp=K$ and $np=N$. If $\theta$ is a Gamma prior distribution $G(a, b)$ then, (see (Robert, 1992)) the posterior of $\theta$, given $\omega'$, is a Gamma distribution $G(a+K, b+\omega')$. The index of satisfaction is

$$\phi(\omega'')=0 \ \text{ if } \ \omega'' \le q_0$$

$$= F(\omega'') = \int_0^{\omega''} \frac{\theta_0^N}{\Gamma(N)} e^{-\theta_0 t} \, t^{N-1} \, dt \ \text{ else,} \tag{13}$$

where $q_0$ is defined by: $F(q_0) = 1-\alpha$.
Then,

$$l(\omega',\omega'') = \frac{\Gamma(K+N+a)}{(\omega'+\omega''+b)^{K+N+a}} \times \frac{\omega'^{K-1} \,.\, \omega''^{N-1} \,.\, b^a}{\Gamma(K).\Gamma(N).\Gamma(a)} \tag{14}$$

and

$$v\ (\omega''/\omega') = \frac{\omega''^{N-1}}{(\omega'+\omega''+b)^{K+N+a}} \times \frac{1}{\displaystyle\int_0^{\infty} \frac{\omega''^{N-1}}{(\omega'+\omega''+b)^{K+N+a}} d\omega''} \tag{15}$$

Finally, the prediction of satisfaction is given by:

$$\pi(\omega') = \int_{q_0}^{+\infty} \left[ \int_0^{\omega''} \frac{\theta_0^K}{\Gamma(N)} e^{-\theta_0 u} \, u^{N-1} \, du \right] v(\omega''/\omega') \, d\omega'' \tag{16}$$

which can be estimated numerically.

4.2. *Binomial distribution*

Let us suppose that $X_1^{'}, ..., X_k^{'}$ and $X_1^{''}, ..., X_n^{''}$ are *i.i.d.* random variables of binomial distribution $B(s, \theta)$ where $\theta$ is unknown and $s$ is known. Then, $\omega' = \sum_{i=1}^{k} X_i^{'}$ and $\omega'' = \sum_{i=1}^{n} X_i^{''}$ are the binomial distributions $B(ks, \theta)$ and $B(ns, \theta)$, respectively.

Let be $ks=K$ and $ns=N$.

Let us suppose that $\theta$ has as prior distribution a Beta distribution of parameters $a$ and $b$. Consequently (Robert, 1992) $\theta$, given $\omega'$, is a Beta distribution of parameters $a+\omega'$ and $K+b-\omega'$. Thus, while posing

$$\beta(x, y) = \frac{\Gamma(x).\,\Gamma(y)}{\Gamma(x+y)}, \tag{17}$$

it follows, for any $(\omega', \omega'') \in \{0, 1, ..., K\} \times \{0, 1, ..., N\}$,

$$l(\omega', \omega'') = \frac{C_K^{\omega'}.C_N^{\omega''}}{\beta(a,b)}.\beta(a+\omega'+\omega'',\ b+K+N-\omega'-\omega'') \tag{18}$$

and

$$v(\omega''|\omega') = \frac{C_N^{\omega''}.\beta(a+\omega'+\omega'', b+K+N-\omega'-\omega'')}{\sum_{\omega''=0}^{N} C_N^{\omega''} \beta(a+\omega'+\omega'',\ b+K+N-\omega'-\omega'')}. \tag{19}$$

The index of satisfaction is given by:

$$\begin{aligned} \phi(\omega'') &= 0 \quad \text{if } \omega'' < q_0 \\ &= \sum_{t=0}^{\omega''-1} C_N^t \ \ \theta_0^t \ (1-\theta_0)^{N-t} \quad \text{if } \omega'' \text{ is an integer and } \omega'' \geq q_0, \end{aligned} \tag{20}$$

where

$$q_0 = \inf\left\{u;\ \sum_{t=u}^{N} C_N^t \ \ \theta_0^t \ (1-\theta_0)^{N-t} \leq \alpha \right\}. \tag{21}$$

Finally, the prevision of satisfaction is

$$\pi(\omega') = \sum_{\omega''=q_0}^{N} \sum_{t=0}^{\omega''-1} C_N^t \ \ \theta_0^t \ (1-\theta_0)^{N-t} \frac{C_N^{\omega''} \beta\ (a+\omega'+\omega'',\ b+K+N-\omega'-\omega'')}{\sum_{\omega''=0}^{N} C_N^{\omega''} \beta\ (a+\omega'+\omega'',\ b+K+N-\omega'-\omega'')}. \tag{22}$$

4.3. *Poisson sampling*

Let us suppose that $X_i^{'}(1 \le i \le k)$ and $X_j^{"}(1 \le j \le n)$ are *i.i.d.* normal random variables of Poisson distribution *P*($\theta$) where $\theta$ is unknown. Then, $\omega' = \sum_{i=1}^{k} X_i^{'}$ and $\omega" = \sum_{i=1}^{n} X_i^{"}$ are the Poisson distributions *P*($k\theta$) and *P*($n\theta$), respectively.

If $\theta$ is a Gamma prior distribution of parameters *a* et *b* then, the posterior, $\theta$, given $\omega'$, is a Gamma distribution of parameters $a+\omega'$ and $b+k$. The index of satisfaction is then expressed as

$$\begin{aligned} \phi^{"(\alpha)}(\omega") &= 0 \ \text{ if } \ \omega" < q_0 \\ &= \sum_{s=0}^{\omega"-1} e^{-n\theta_0} \ \frac{(n\theta_0)^s}{s!} \ \text{ if } \ \omega" \ge q_0 , \end{aligned} \tag{23}$$

where

$$q_0 \;=\; \inf\left\{ u \;;\; \sum_{s=0}^{u-1} e^{-n\theta_0} \ \frac{(n\theta_0)^s}{s!} \;\ge\; 1 \;-\; \alpha \right\}, \tag{24}$$

and the prevision of satisfaction is given by:

$$\pi(\omega') = \sum_{\omega"=q_0}^{\infty} \sum_{s=0}^{\omega"-1} e^{-n\theta_0} \frac{(n\theta_0)^s}{s!} \cdot \frac{n^{\omega"}}{\omega"!} \cdot \frac{\Gamma(a+\omega'+\omega")}{(b+k+n)^{a+\omega'+\omega"}} \cdot \frac{1}{\sum_{\omega"=0}^{\infty} \frac{n^{\omega"}}{\omega"!} \frac{\Gamma(a+\omega'+\omega")}{(b+k+n)^{a+\omega'+\omega"}}} . \tag{25}$$

4.4. *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 being realizable by the Monte-Carlo methods.

We perform independent observations and of same normal random variable $N(\theta, \sigma^2)$. In all that follows, $\Phi$ (resp. $\varphi$) indicates the cumulative distribution function (resp. the density) of the distribution $N(0, 1)$.

The first result, $\omega'$, is a series ($x_1$, ..., $x_k$) of $k$ observations and the second result, $\omega''$, is a series ($y_1$, ..., $y_n$).

For obvious reasons of exhaustiveness 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 distributions $N(\theta, \sigma_1^2)$ and $N(\theta, \sigma_2^2)$, respectively, where $\sigma_1^2 = \frac{\sigma^2}{k}$ and $\sigma_2^2 = \frac{\sigma^2}{n}$.

We suppose here $\sigma^2$ being known. $\theta$ is unknown, and we choose as a prior distribution for $\theta$ the natural conjugate (Robert, 1992), *i.e.* here the normal distribution $\mu=N(\delta,\ \tau^2)$. We wish to test a null assumption of type $\theta\leq\theta_0$. The distribution of the result $y$ is obviously stochastically increasing in $\theta$.

We use here a usual test ranging on $y$, whose critical region is $]q_0,+\infty[$, where $q_0=\theta_0\ +\ \sigma_2\ u_\alpha^+$, $u_\alpha^+$ indicating the upper $\alpha$ quantile of the standard normal distribution $N(0,1)$: $\Phi(u_\alpha^+)=1-\alpha$. The prevision of satisfaction is given by

$$\pi(x)=\int_{q_0}^{+\infty} L\left(1-\Phi\left(\frac{y-\theta_0}{\sigma_2}\right)\right) f_x(y)dy \tag{26}$$

where $f_x(y)$ is the conditional distribution density of $y$ knowing $x$.

One quotes that, being $\sigma_1^2$, $\sigma_2^2$, $\delta$, $\alpha$ and $x$ given, one wants to calculate

$$\pi(x)=\frac{1}{s}\int_{q_0}^{+\infty} L\left(1-\Phi\left(\frac{y-\theta_0}{\sigma_2}\right)\right)\varphi\left(\frac{y-m}{s}\right) dy \tag{27}$$

where $m=\dfrac{\tau^2x+\sigma_1^2\delta}{\sigma_1^2+\tau^2}$, $s^2=\sigma_2^2+\dfrac{\tau^2\sigma_1^2}{\sigma_1^2+\tau^2}$, $q_0=\theta_0+\sigma_2u_\alpha^+$.

By change of variable, one obtains

$$\pi(x)=\int_{-bx'+d\theta'_0+tu_\alpha^+}^{\infty} L\left(1-\Phi\left(\frac{z-(-bx'+d\theta'_0)}{t}\right)\right) \varphi(z)dz \tag{28}$$

where $x'=\dfrac{x-\delta}{\tau}$, $\theta_0'=\dfrac{\theta_0-\delta}{\tau}$, $\sigma'_1=\dfrac{\sigma_1}{\tau}$, $\sigma'_2=\dfrac{\sigma_2}{\tau}$,

$b=[(1+\sigma'^2_1)\ (\sigma'^2_1+\sigma'^2_2+\sigma'^2_1\,\sigma'^2_2)]^{-\frac{1}{2}}$, $d=(1+\sigma'^2_1)b$, $t=\sigma'_2\,d$.

It is noted that $\pi(x)$ only depends of the three real numbers which we will call *essential parameters*: two parameters of scale, $d$ and $t$, in the expressions of which intervene only the ratios of variances $\dfrac{\sigma_1^2}{\tau^2}$ and $\dfrac{\sigma_2^2}{\tau^2}$ and a location parameter $a=-bx'+d\theta'_0$.

At threshold α and at fixed scale parameters, a modification of $\theta_0$ and $\delta$ has a translation effect on $\pi(x)$: if $\theta_0'$ increases by $\Delta\theta_0'$, the representing curve of $\pi$ undergoes a horizontal adjustment of amplitude $\dfrac{d}{b}\ \Delta\theta_0'$ where $\dfrac{d}{b}=1+\sigma'^2_1$.

In order to carryout the calculations of $\pi(x)$ using a Monte-Carlo method, we rewrite $\pi(x)$ in the form

$$\pi(x) = [1-\Phi(a+tu_\alpha^+)] \int_{\Re} L\left(1-\Phi\left(\frac{z-a}{t}\right)\right) \frac{\varphi(z)}{1-\Phi(a+tu_\alpha^+)} 1_{\left[a+tu_\alpha^+,\, \infty\right[}(z)\, dz, \quad (29)$$

where $\dfrac{\varphi}{1-\Phi(a+tu_\alpha^+)} 1_{\left[a+tu_\alpha^+,\, \infty\right[}$ is the probability density $Q$, deduced from the cumulative distribution function of the standard normal distribution by conditioning by the event $[a+tu_\alpha^+,\, \infty[$ .

The Monte-Carlo method then consists in approaching $\pi(x)$ by

$$[1-\Phi(a+tu_\alpha^+)]\left[\frac{1}{N}\sum_{i=1}^{N} L\left(1-\Phi\left(\frac{Z_i-a}{t}\right)\right)\right], \quad (30)$$

where the $Z_i$ are $N$ realizations 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],
- $V_i = \Phi(a+tu_\alpha^+) + (1-\Phi(a+tu_\alpha^+))U_i$ , *i.e.*, that $V_i$ follows the uniform distribution on $[\Phi(a+tu_\alpha^+), 1]$,
- $Z_i = \Phi^{-1}(V_i)$, i.e., that $Z_i$ follows the distribution $Q$.

One will find below the representative curves of $\pi$ as a function of the observation $x = \dfrac{1}{k}\sum_{i=1}^{k} x_i$ . We have taken in each graph $\delta$=0 and $\tau$=1, which does not diminish of anything the general information since essential parameters depend only on $x$ and $\theta_0$ via $x' = \dfrac{x-\delta}{\tau}$ and $\theta'_0 = \dfrac{\theta_0-\delta}{\tau}$. We have considered only the case $\theta_0$=0 considering that a modification of $\theta_0$ will only result in a translation effect. From one graph to another thus vary the variances $\sigma_1^2$ and $\sigma_2^2$ . A value of 0.05 is adopted for $\alpha$. We have considered situations for $\sigma_1^2$ and $\sigma_2^2$ where, in the first as in the second sample, the observations are of the same unit variance $\sigma^2$, but where the numbers can vary. We have taken:

- on the one hand $\sigma^2$=1 and $\sigma^2$=4 (in other words the ratio of the standard deviation of the observations to the standard deviation of the prior is 1 or 2),

- on the other hand, $k$=10 and $n$=10 or 20 (in other words the ratio of the numbers of the second step eventual to the first explorative step is 1 or 2).

The graphs (1-4) represent the prevision of satisfaction when $L(p)=(1-p)^l$ for $l$=1. We have indicated in each time the essential parameters which are: the value of $t$ and a bilinear form which is the expression of $a$ as a function of $x$ and $\theta_0$. For each of the four situations given in table 1 are represented on the same graph (for $\theta_0$=0, $\alpha$=0.05 and $N$=50), the curves of the prevision of satisfaction relative to indices $S_{1,\alpha}$ and $S_{0,\alpha}$ defined for $l$=1 and $l$=0. These curves are given on Figures (5-8).

One can see that these curves are very close, but they break away when $x$ is rather large, *i.e.*, superior to $\theta_0$, which conveys well the interest of the consideration of the $p$-value in the index of satisfaction that the only rejection of the assumption is all the more informative since $x$ is larger, which proves well that the index that we propose is better.

TABLE 1

| n | $\sigma^2 = 1$ | $\sigma^2 = 4$ |
|---|---|---|
| 10 | $\sigma_1^2 = 0.1$ ; $\sigma_2^2 = 0.1$ | $\sigma_1^2 = 0.4$ ; $\sigma_2^2 = 0.4$ |
| 20 | $\sigma_1^2 = 0.1$ ; $\sigma_2^2 = 0.05$ | $\sigma_1^2 = 0.4$ ; $\sigma_2^2 = 0.2$ |

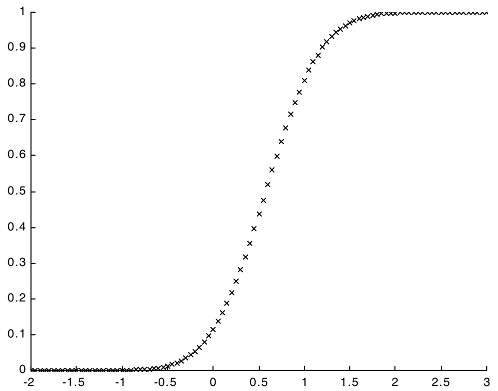

*Figure 1* – Prevision of satisfaction for $l = 1$. Data: $\alpha = 0.05$; $\delta = 0$; $\tau = 1$, $\sigma^2 = 1$; $k = 10$; $n = 10$; (therefore $\sigma_1^2 = 0.1$; $\sigma_2^2 = 0.1$). Essential parameters: $t = 0.724$; $a = -2.0806x + 2.28870_0$. Graph with a step of 0.05 for $x$

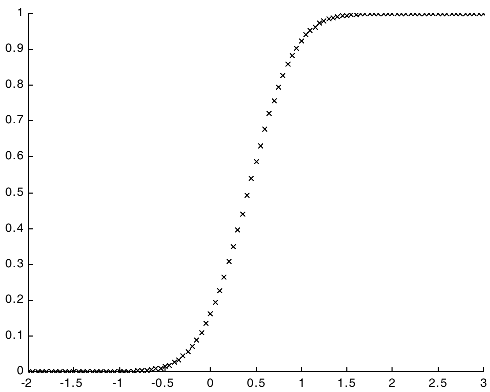

*Figure 2* – Prevision of satisfaction for $l = 1$. Data: $\alpha = 0.05$; $\delta = 0$; $\tau = 1$, $\sigma^2 = 1$; $k = 10$; $n = 20$, (therefore $\sigma_1^2 = 0.1$; $\sigma_2^2 = 0.05$). Essential parameters: $t = 0.596$ ; $a = -2.4218x + 2.664\theta_0$. Graph with a step of 0.05 for $x$.

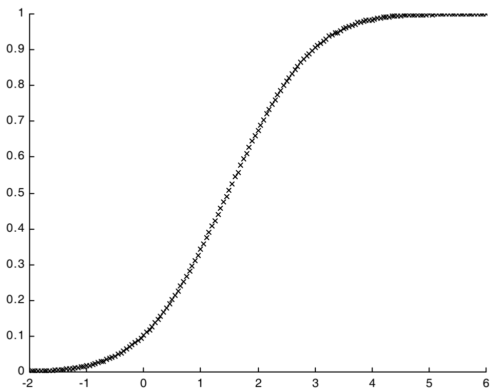

*Figure 3* – Prevision of satisfaction for $l = 1$. Data : $\alpha = 0.05$; $\delta = 0$, $\tau = 1$; $\sigma^2 = 4$, $k = 10$, $n = 10$ (therefore $\sigma_1^2 = 0.4$; $\sigma_2^2 = 0.4$). Essential parameters: $t = 0.764$; $a = -0.8626x + 1.2076\theta_0$. Graph with a step of 0.05 for $x$.

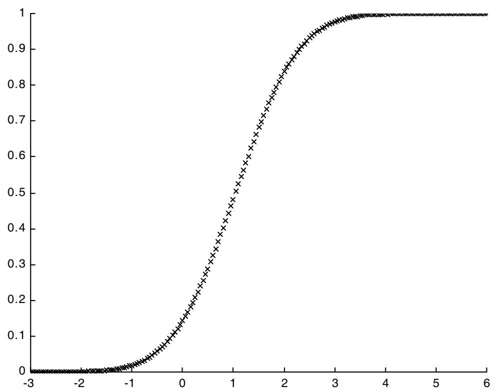

*Figure 4* – Prevision of satisfaction for $l = 1$. Data: $\alpha = 0.05$; $\delta = 0$; $\tau = 1$; $\sigma^2 = 4$; $k = 10$; $n = 20$; (therefore $\sigma_1^2 = 0.4$; $\sigma_2^2 = 0.2$). Essential parameters: $t = 0.642$; $a = -1.0249x + 1.4349\theta_0$. Graph with a step of 0.05 for $x$.

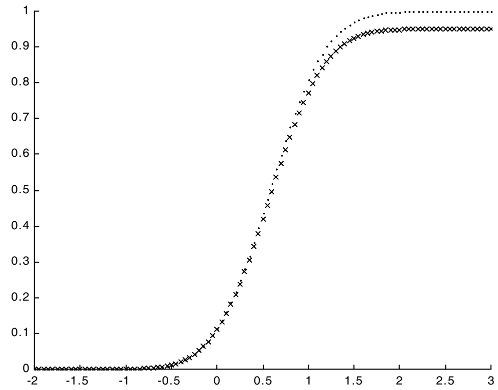


*Figure 5* – Prevision of satisfaction relative to $S_{1,\alpha}$ = ····· ; Prevision relative to $S_{0,\alpha}$ =××××
Data: $\alpha = 0.05$; $\sigma_1^2 = 0.1$; $\sigma_2^2 = 0.1$.
Graph with a step of 0.05 for $x$.

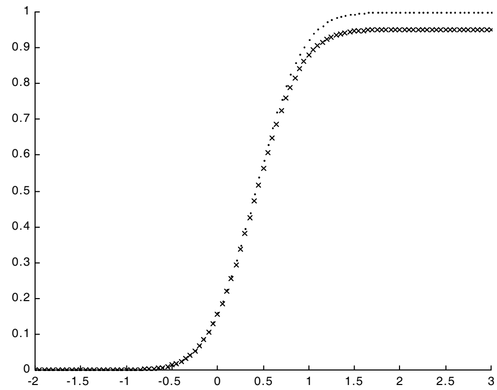


*Figure 6* – Prevision of satisfaction relative to $S_{1,\alpha}$ = ····; Prevision relative to $S_{0,\alpha}$ =××××
Data: $\alpha = 0.05$; $\sigma_1^2 = 0.1$; $\sigma_2^2 = 0.05$.
Graph with a step of 0.05 for $x$.

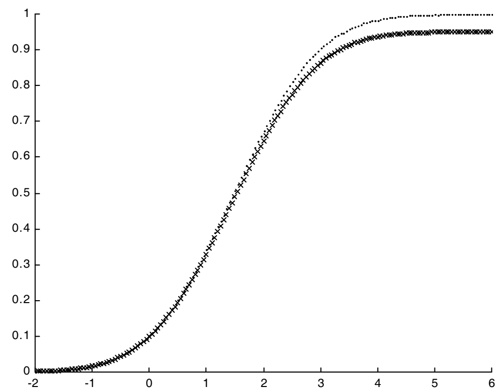


*Figure 7* – Prevision of satisfaction relative to $S_{1,\alpha}$ = ····; Prevision relative to $S_{0,\alpha}$ =××××
Data: $\alpha = 0.05$; $\sigma_1^2 = 0.4$; $\sigma_2^2 = 0.4$.
Graph with a step of 0.05 for $x$.

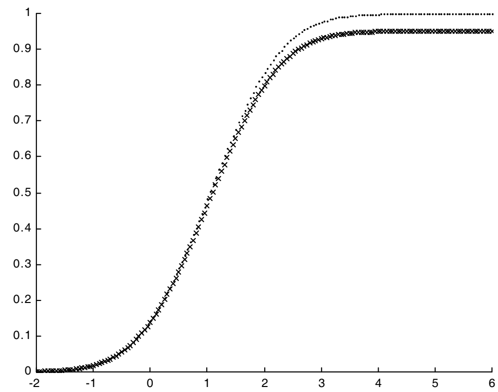


*Figure 8* – Prevision of satisfaction relative to $S_{1,\alpha}$ = ····; Prevision relative to $S_{0,\alpha}$ =××××
Data: $\alpha = 0.05$; $\sigma_1^2 = 0.4$; $\sigma_2^2 = 0.2$.
Graph with a step of 0.05 for $x$.

## 5. CONCLUSION

The main contribution of this paper was to apply the Bayesian predictive procedure to a family of limited indices of satisfaction. This approach was considered for monitoring the chances that a two-steps inferential procedure will show a conclusive result (in this case the rejection of a statistical hypothesis). These indices generalize the "rudimentary" index of satisfaction considered by Grouin (1994) and Lecoutre et al. (1995), which corresponds to the indicator function of the critical region of the statistical test. This is an important innovation, since the prevision index associated to the indicator function of the critical region is easier to compute and it may be fruitfully considered by an expert in order to decide for the continuation of the experiment. It was noted from the computations and simulation results that the improved index of satisfaction is that which does meet best (owing to the consideration of the *p*-value) simplicity and stability requirements in calculations (this *p*-value being directly used without taking some function of this *p*-value other than identity).

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## RIASSUNTO

*Indice e previsione di soddisfazione nei modelli esponenziali per le prove cliniche*

In questo articolo vengono proposti indici di soddisfazione e di previsione di soddisfazione relativi ad una prova d'ipotesi nel caso di una procedura in due tappe, cosa che è spesso realizzata nei protocolli di prove cliniche. Utilizziamo una costruzione di modelli bayesiani per valutare esplicitamente o numericamente la previsione di soddisfazione per molti modelli esponenziali quando la legge a priori del parametro è una legge a priori combinata.

## SUMMARY

*Index and prevision of satisfaction in exponential models for clinical trials*

This paper deals with a Bayesian predictive approach applied to a frequentist statistical test. The methodology is useful in two-steps testing procedures, such as those considered in the clinical trial context. We review the Bayesian predictive procedure for monitoring experiments and the notion of index of satisfaction. We applied this procedure to a family of limited indices of satisfaction. These indices generalize the rudimentary index of satisfaction considered by Grouin (1994) and the interest of these indices of satisfaction could be in the concept of "prevision of satisfaction" for a future sample, given the data in

hand. 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"). The procedure is introduced in the case of a two-step trial, where the result of the first step is used to decide if the experiment will be continued. We consider different cases of the application of the proposed procedure with a conjugate prior. The computations and the simulation results concern an inferential problem, related to the Gaussian model.