On a class of predictive distributions of interest in monitoring clinical trials

Su alcune distribuzioni predittive di interesse nel monitoraggio delle prove cliniche

Lilla Di Scala¹
Università di Pavia
Dipartimento di Matematica
lilla@dimat.unipv.it

Mauro Gasparini²
Politecnico di Torino
Dipartimento di Matematica
mauro.gasparini@polito.it

Riassunto: In questo lavoro si espone una visione bayesiana, avente carattere predittivo, delle procedure statistiche di decisione adottate nell’ambito delle prove cliniche. Questo approccio predittivo, sussidiario rispetto alle tecniche inferenziali classiche, conduce alla definizione di classi di densità con supporto $[0, 1]$ di interesse generale, oltre che di rilievo nel monitoraggio delle prove cliniche. Si presenta una di tali classi, derivante da un disegno di prova clinica piuttosto comune, evidenziandone la flessibilità.

Keywords: clinical trial; predictive density; expected power.

1. Bayesian evaluation of a clinical trial

In a recent book, Spiegelhalter et al. (2004) illustrate different Bayesian methods for the analysis and the routine evaluation of a wide range of medical and health-care problems. Aside from the philosophical arguments which used to distinguish the defence of the Bayesian paradigm up to a few years ago, the point of view put forth in this paper is purely practical. The methodology presented is not openly in contrast with traditional and well-established statistical methods. Rather, it fulfils the request coming from clinicians, health authorities and researchers to integrate experimental evidence with information and judgements coming from external sources and going beyond the single study horizon.

One of the most important sources of information for such Evidence-Based Medicine is certainly the randomized clinical trial, to which a considerable part of the above-mentioned work is devoted. Since much of the present-day clinical trial methodology is non-Bayesian, the authors do not advocate an alternative Bayesian set-up but believe in a hybrid approach which may include both the classical concepts of test, alternative hypothesis, power, and also Bayesian elements such as predictive analysis, Bayes factor and weight of evidence.

Within this context, it is then appropriate to consider the concept of predictive power, defined as the Bayesian evaluation of the probability that a clinical trial, carried out according to classical methodology, will lead to a significant result. Such predictive power, also called expected power, was originally proposed by Spiegelhalter’s group (Spiegelhalter et al. (1986)), later revisited by various authors and, lastly, taken up again in Gasparini et al. (2003), which contains some relevant references.

This short paper investigates the classes of predictive distributions which stem from the applied context described in Gasparini et al. (2003).

¹Indirizzo per corrispondenza: Via Ferrata 1, 27100 Pavia
The clinical trial context in this paper is exemplified as follows: a Bayesian statistical model is set-up in which a random variable $\delta$, representing the parameter of interest, is distributed according to a certain probability distribution $P$. Note that $P$ depends on the state of information at the current stage of the trial. Success of the trial is defined as the event $S = \text{"rejecting the null hypothesis } H_0\text{"}$. Therefore, predictive power is formally defined as

$$
\mathbb{E}_P[\pi(\delta)] = \mathbb{E}_P[\mathbb{P}(S | \delta)]
$$

that is, the expectation of power $\pi(\delta)$, which is the conditional probability of success given $\delta$. In this context, power $\pi$ is a random variable and its distribution will be termed predictive distribution.

In particular, the scenario chosen in this paper to describe the above concepts is that of a superiority trial with parallel design in which a continuous endpoint is normally distributed with known variance and mean $\delta$, representing the parameter of interest and being itself normal. Such may be the case when dealing with two populations, for example patients receiving treatment or control, being compared on the basis of a continuous variate.

2. A class of predictive distributions

The logical process which leads to predictive distributions automatically generates new classes of distributions, as illustrated in Lecoutre (1999). In this section it will be shown how, in particular, the concept of predictive power is associated to some new probability distributions which were unknown up to now, to these authors’ knowledge, and could be of interest also in other applied contexts.

Assume the trial is at planning stage, when no data has yet been collected. Let the primary endpoint be $D \sim N(\delta, s^2)$ and suppose that a significant result from the trial would be to reject the hypothesis $H_0 : \delta \leq \delta_0$. Assume that $c_\alpha$ is the critical value of the test of level $\alpha$ established according to standard hypothesis testing procedures. Then $S = \{D > c_\alpha\}$. Let $\delta \sim N(\theta, \tau^2)$ be the prior distribution. In this case, it follows that the density of the random variable $\pi(\delta) = \mathbb{P}(D > c_\alpha | \delta)$ is in a class of univariate probability distributions with support $[0, 1]$ parameterized by the known quantities defining the clinical trial at hand, i.e. $\delta_0, \alpha, \theta, \tau^2$ and $s^2$. These densities have an analytical expression as follows

$$
f_\pi(p) = s \cdot \phi(c_\alpha - s\Phi^{-1}(1-p)|\theta, \tau^2) / \phi(\Phi^{-1}(1-p))
$$

for $p \in [0, 1]$, where $\Phi(\cdot|\mu, \sigma^2)$ is the cdf of a normal distribution with mean $\mu$ and variance $\sigma^2$, $\phi(\cdot|\mu, \sigma)$ is its associated density and $\Phi^{-1}(\cdot|\mu, \sigma)$ its quantile function. If $\mu$ and $\sigma$ are not specified, the standard normal is to be intended. See Gasparini et al. (2003) for details on how to derive $F_\pi$, cumulative distribution of $\pi$, from which $f_\pi$ is obtained.

The family of probability distributions with density $f_\pi$ shows quite a good flexibility, as the parameters vary in their domain of definition. In fact, depending on the ratio $s^2/\tau^2$, the predictive density may acquire the following shape: unimodal (if $s^2/\tau^2 > 1$), "bathtub" shape (if $s^2/\tau^2 < 1$) and monotone (if $s^2/\tau^2 = 1$). In the latter case, $f_\pi$ is monotone increasing (decreasing) if $\theta > c_\alpha$ ($\theta < c_\alpha$) and $f_\pi$ is the uniform density on $[0, 1]$ if $\theta = c_\alpha$. Hence, $f_\pi$’s shape is determined by the relationship between the variance of the observable, that is $s^2$, and the prior variance $\tau^2$. As $\tau^2 \to 0$, keeping $s^2$ fixed, the prior will become more peaked and consequently $f_\pi$ will do the same, while if $\tau^2 \to \infty$, as
the prior tends to flatten itself, $f_\pi$ will give more mass to the extreme values 0 and 1, conveying the uncertainty about the outcome of the trial.

Figure 1 shows the three possible shapes of $f_\pi$ based on different values of the ratio $s^2/\tau^2$. Three priors have been chosen according to the prescription contained in Spiegelhalter et al. (1994): a skeptical prior centered in $\delta_0 = 0$, an optimistic one centered in an alternative $\delta_A = 10$ and a “middle-of-the-road” one centered in $(\delta_0 + \delta_A)/2$. For all three, $\tau^2$ was obtained by setting the prior probability of $\{\delta < \delta_0\}$ under the skeptical prior equal to $\alpha = 0.05$. Three values for $s^2$ were then chosen and the corresponding predictive densities calculated. Note that when $s^2/\tau^2 < 1$, the “bathtub” distribution is such that predictive power is not a good summary of $f_\pi$ and the decision-maker might be misled if the entire distribution were not drawn. Moreover, the choice of different priors may aid in understanding how the situation is sensitive to prior judgement.

Specifically, as $f_\pi$ may be sensitive to the choice of prior variance, it could be of interest to assign a hyper-prior on $\tau^2$. A standard way to do so is to let $\tau^{-2} \sim \Gamma(a, b)$, with $a, b > 0$. In this hierarchical model, which is equivalent to imposing a Student $t$ prior distribution on $\delta$, it holds that

$$f_\pi(p) = s \cdot f_t \left( c_\alpha - s \Phi^{-1}(1 - p) | \theta, ab^{-1}, 2a \right) / \phi \left( \Phi^{-1}(1 - p) \right),$$

where $f_t$ is the density of a Student $t$ distribution; refer to Bernardo and Smith (2000) for the intended parametrisation. The class of predictive distributions thus obtained is such that $f_\pi(p) \to \infty$ both as $p \to 0$ and as $p \to 1$.

The methodology described in the current section was discussed during the planning of a trial for the study of a new therapy meant to reduce diastolic blood pressure (DBP). Standard treatment, with which comparison was intended, is known to reduce DBP from baseline by 7 mm/hg after 8 weeks on average, while the sponsor was hoping that the new therapy would reduce it by an extra 3 mm/hg. After setting the prior parameters for this specific context, analysis of predictive power and distribution was thus used in the trial design in order to study the chances of rejecting the hypothesis of clinical indifference $H_0: \delta \leq 0$.

3. At Interim Bayesian Evaluation of a Clinical Trial

Predictive densities of the same class are obtained when an interim analysis is planned and evaluated at interim stage, see Gasparini et al. (2003). Assume that $D_1$ has been observed and that $\delta | D_1 \sim N(\theta_1, \tau^2)$ according to standard normal conjugate analysis. The predictive density at interim $f_{\pi}^I$ is thus

$$f_{\pi}^I(p) = s_2 \cdot \phi \left( \left[ n_1 n_2^{-1} \left( c_\alpha - D_1 \right) + c_\alpha^I \right] - s_2 \Phi^{-1}(1 - p) | \theta_1, \tau^2 \right) / \phi \left( \Phi^{-1}(1 - p) \right),$$

where $c_\alpha^I$ is such that success is $S = \{D > c_\alpha^I\}$, $n_1 = n - n_2$ is the sample size observed at interim and $s_2^2$ is the variance of $D_i$, $i = 1, 2$, with $D = n_1 \bar{D}_1 + n_2 \bar{D}_2$. Note that $f_{\pi}^I$ differs from $f_\pi$ in that the prior parameters are replaced by the updated ones and $c_\alpha$ is replaced by a linear combination of the critical value of the test $c_\alpha^I$ and the observed $D_1$, thus changing the relationship of dependence from the trial’s parameters. Although the analytical expression is essentially the same, this case is very important because interim evaluation is a critical tool for the monitoring of clinical trials.
In particular, it is of interest to consider the case in which an improper prior is chosen for $\delta$. In fact, as $\tau^2 \to \infty$, $\theta_1 \to D_1$ and $\tau_1^2 \to s_1^2$, it follows that
\[
f_{\pi}(p) \to \frac{s_2 \cdot \phi \left( [n_1n_2^{-1} (c_1^1 - D_1) + c_1^0] - s_2\Phi^{-1}(1-p)|D_1, s_1^2) \right)}{\phi \left( \Phi^{-1}(1-p) \right)}.
\]
Consequently, the role of the ratio $s^2/\tau^2$ at planning stage is played here by $s_2^2/s_1^2$: when the variance of what is still to be observed, that is $D_2$, is greater than that of the already observed difference $D_1$, then the predictive density is unimodal and judgement may be more clear-cut. Typically, as in the treatment/control scenario, the variances $s_i^2$ are functions of the sample sizes and of the known inter-patient variance $\sigma^2$ in a way that $s_2^2/s_1^2$ is a function of the sole sample sizes. Note how the observations making up $D_1$ practically act as a training set in the absence of a proper prior, therefore allowing to compute a prior-free predictive power at interim stage.

**Figure 1:** Different shapes for $f_{\pi}$.

![Figure 1](image.png)

**References**