Skeptical and Optimistic Robust Priors for Clinical Trials

Ensayos clínicos bajo un enfoque bayesiano robusto con previas escépticas y optimistas

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Abstract

A useful technique from the subjective Bayesian viewpoint, is to ask the subject matter researchers and other parties involved, such as pharmaceutical companies and regulatory bodies, for reasonable optimistic and pessimistic priors regarding the effectiveness of a new treatment. Up to now, the proposed skeptical and optimistic priors have been limited to conjugate priors, though there is no need for this limitation. The same reasonably adversarial points of view can take with robust priors. Robust priors permit a much faster and efficient resolution of the disagreement between the conclusions based on skeptical and optimistic priors. As a consequence, robust Bayesian clinical trials tend to be shorter. Our proposal in this paper is to use Cauchy and intrinsic robust priors for both skeptical and optimistic priors leading to results more closely related with the sampling data when prior and data are in conflict. In other words, the use of robust priors removes the dogmatism implicit in conjugate priors. Dogmatism here has very precise meaning: Conjugate priors affect the posterior conclusions by a fixed rate, regardless if there is a conflict between prior and data. Robust priors are automatically discounted by Bayes Theorem in the presence of conflict.

Key words: Clinical trials, Bayesian robustness, Prior distribution.

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Resumen

Ensayos clínicos bajo un enfoque de estadística Bayesiana están adquiriendo cada vez mayor importancia. Anteriormente se sugirió una idea que ha dado ventaja al uso de previas bayesianas: suponer dos densidades a priori con información muy distinta sobre la efectividad de un nuevo tratamiento: una previa escéptica que refleje pesimismo sobre la superioridad del tratamiento nuevo. Esta es la posición de los organismos reguladores que autorizan o no los nuevos medicamentos que deben ser vendidos en el mercado. También proponen una densidad previa optimista (o "entusiasta") que refleja la posición de los investigadores y compañías farmacéuticas que proponen el nuevo tratamiento. Esta diversidad de opiniones es sumamente útil y queremos preservarla. En la propuesta original, sin embargo, se supone que la forma funcional de las densidades previas es normal, lo cual es más simple de analizar y asignar. Infortunadamente, la simplicidad exige un precio muy grande. Para que haya acuerdo entre los dos análisis se necesita muchísima información muestral. En este artículo se propone mantener las dos previas que representan puntos de vista adversos, pero con una forma funcional de colas gruesas, como la densidad Cauchy. Las previas robustas permiten una resolución del desacuerdo de forma más rápida y eficiente; por tanto, los ensayos clínicos tienden a ser más cortos. Se asume un concepto de dogmatismo muy preciso: las previas conjugadas afectan las conclusiones en una tasa fija, sin importar si hay conflicto entre la verosimilitud y la densidad previa. Además, las previas robustas de colas gruesas son automáticamente descontadas en presencia de conflicto, por el teorema de Bayes en favor de la información dada por los datos.

Palabras clave: distribución *a priori*, ensayos clínicos, robustez bayesiana.

1. Introduction

Clinical trials are contentious. Pharmaceutical companies are eager to show that their new drug, on which they may have been invested millions of dollars, is a substantial improvement over the current treatment. Government regulatory agencies take the opposite view and ask for substantial evidence that the new drug is not less effective than the current standard.

Bayesian statistics permits a useful technique for modeling adversarial positions by using *two* prior distributions on the parameters of interest. One, the optimistic prior, corresponds to positive expectations. The other, the pessimistic prior, corresponds to a more skeptical position.

To be more specific, let us consider the following one-sided hypothesis test. Suppose that we have two medical treatments with corresponding probabilities of events p_1 and p_2. The events may be for instance "disease recurrence" or "deaths". The Odds Ratio is defined as

$$OR = \frac{p_1/(1 - p_1)}{p_2/(1 - p_2)}$$

and to make the assumption of normality more realistic, the focus is on the parameter $\theta = \log(OR)$. Often the test of interest is the following:

$$H_0 : \theta \geq \theta_H, \; vs \; H_1 : \theta < \theta_H \tag{1}$$

Here, H_1 is the region of substantial improvement achieved by the new treatment over the standard one. Here, $\theta_H < 0$, corresponding to $OR < 1$, for example $OR = 0.5$, the point of 50% of improvement.

Part of the clever proposal by Spiegelhalter, Abrams & Myles (2004) is to assume two priors: π_S and π_O. The skeptical position (say the government regulatory body attitude) is to first center the prior on the point of no difference, i.e. $\theta = 0$, and secondly to give only a small probability, denoted by ξ, say $\xi = 0.05$ or $\xi = 0.025$ to the improvement (i.e H_1), that is

$$P_S(H_1) = \int_{-\infty}^{\theta_H} \pi_S(\theta)d\theta = \xi \tag{2}$$

The optimistic position is centered on θ_H and it gives only probability ξ that there is no benefit with the new treatment (the investigator position), so

$$P_O(\theta > 0) = \int_0^{\infty} \pi_0(\theta)d\theta = \xi \tag{3}$$

If under the skeptical prior, the posterior probability of H_1 is larger than $1 - \gamma$, say $1 - \gamma = 0.95$, that is, if under the skeptical prior $P(H_1 \mid \text{Data}, \pi_S) > 1 - \gamma$, then to decide in favor of H_1 is safe. If with the optimistic prior $P(\theta > 0 \mid \text{Data}, \pi_O) > 1 - \gamma$, to decide that there is not benefit with the new treatment is safe. If there is disagreement between the procedures then the trial is inconclusive, given the information so far collected.

This approach is intuitively satisfying. However, this framework may be overly cautious and lead to an enormous delay in the decisions. The implementation proposed in Spiegelhalter et al. (2004) uses conjugate priors, which lead to simple computations. However, we show in this article that we may preserve the useful framework of skeptical and optimistic priors without the dogmatism inherent in conjugate priors.

Pericchi & Smith (1992) showed some aspects of the robustness of the Student-t prior for a normal location parameter and provided approximations to the posterior moments in the model Student-t/normal. The Cauchy prior, as a Student-t with one degree of freedom, can be used in this context as well. However, for normal log-odds there is a robust prior proposed by Berger (1985) that leads to a closed form posterior and moments, a sort of the "best of both worlds". The "intrinsic prior" was obtained in Berger & Pericchi (1996) as the implicit prior to which the arithmetic intrinsic Bayes factor converges, and it turns out that it is a limiting case of Berger's prior. In Fúquene, Cook & Pericchi (2009), robust priors are proposed for clinical trials. But the priors studied there are clinical priors based on previous trials. Here, we propose a class of robust priors, a novel proposal to the

best of our knowledge, that improves the class of Normal skeptical and optimistic priors originally proposed by Spiegelhalter et al. (2004). Note that the original proposal by Spiegelhalter et al. (2004) propose a class of priors of two elements: the skeptical and the optimistic normal priors. We propose a class of robust priors, again of two elements: the skeptical and the optimistic robust prior. Effectively, however, both these classes allow a substantial variation on prior assessments. We illustrate the improvement in terms of an example and also provide mathematical results that lead us to expect that the speed of convergence of the robust class is substantially higher than the normal class.

2. Illustration: Skeptical and Optimistic Robust Priors

A useful suggestion under the *subjective Bayesian viewpoint*, taken by Spiegelhalter, Freedman & Parmar (1994), is to ask the subject matter researchers, for reasonably optimistic and pessimistic priors (regarding the effectiveness of a new treatment). On the log-odds scale, a skeptical prior on the amount of improvement has mean zero (i.e., no difference between treatments, $\theta = 0$) and a substantial probability that the new treatment is not better. The prior scale is assessed in reference to an optimistic hypothesis θ_H (say $\theta_H = -0.69$, which corresponds to a 50% improvement, see below). Then a small (skeptical) probability ξ is assessed, for example $\xi = 0.025$: that the effect of the treatment is equal or better than θ_H. For the Cauchy prior, the skeptical parameters are very easy to assess. The location μ is zero and the scale $\beta = \theta_H / \tan(\pi(\xi - 1/2))$. In Fúquene et al. (2009), other robust heavy tailed priors are considered, apart from the Cauchy, and several mathematical results are presented. Two such priors are the Intrinsic Prior, calculated by Berger & Pericchi (1996), and the so called Berger's prior (Berger 1985). There is a close relationship between the Intrinsic and Berger's prior, and for the most part we present the results for the Intrinsic prior, for which the location (μ) is zero and the scale, τ, is found by solving the following equation

$$\int_{-\infty}^{\theta_H} \frac{1}{2\sqrt{\pi}} \frac{1 - \exp\left\{-\frac{(\theta - \mu)^2}{\tau^2}\right\}}{(\theta - \mu)^2/\tau} d\theta = \xi \tag{4}$$

For the optimistic priors, the assessments are similar, except that the location is changed to $\mu = \theta_H = -0.69$, that is the location now placed at the point of 50% improvement. The scales are obtained by placing $1 - \xi$ probability on H_1. For example, in equation (3) the right hand side is changed from ξ to $1 - \xi$.

Illustrative example. Suppose that a new drug is compared with a conventional treatment. With the conventional treatment, 26 out of 97 patients died (26.8%). Only 13 out of 193 patients died with the new drug (6.7%). We wish to test the hypothesis that the improvement with the new treatment is at least 50%

of reduction of the odds of death. Is there enough evidence to make a skeptical prior to give over 90% of posterior probability?

We now make the comparison of two analysis: The first combining the normal log odds coupled with a normal skeptical prior (with the current data). Alternatively, we assume heavy-tailed Cauchy and intrinsic priors, with the same location and the same probabilities of the region of interest as the normal prior. Thus we assume that the normal, Cauchy, and intrinsic skeptical priors have all mean $\log(OR) = 0$ and with a 95% interval running from 50% reduction in odds of death $(\log(OR) = -0.69)$ to a 50% increase $(\log(OR) = 0.69)$.

In the normal prior case, we assume $\pi_n(\theta) = N[0, \sigma^2/n_0]$, and n_0 is referred to as "the number of prior observations". On a log(OR) scale, this prior has a 95% interval from -0.69 to 0.69 and so has a standard deviation $0.69/1.96 = 0.35$ (for $\xi = 0.025$) and hence the number of prior observations is $n_0 = 4/0.35^2 = 32.3$.

For Cauchy and intrinsic priors the scale is 0.05 and 0.06 respectively, so that the prior probability of the region on which there is a reduction of risk of 50% or more is 0.025. We use the normal approximation for binary data for the log-odds with the approximate standard error recommended in Spiegelhalter et al. (2004, pp. 26) for 2×2 tables, following their suggestion of an standard error of the likelihood normal and normal/normal posterior model equal to $\sigma = 2$.

As we anticipated above, assume that the evidence arising from the study about 30-day mortality was 26/97 on control and 13/193 on new treatment. If the ratio of the odds of death following the new treatment to the odds of death on the conventional is $OR < 1$ then the data favors the new treatment. We have that the estimated $\log(OR)$ is $\overline{y}_n = -1.6$ ($OR = 0.2$ or 80% risk reduction) with estimated standard error 0.36 and $n = 4/0.36^2 = 30.5$, which in this case is approximately the same weight of the prior $n_0 = 32.3$, as calculated above.

We use the R (R Development Core Team 2009) package named ClinicalRobustPriors, available from the Comprehensive R Archive Network at http://CRAN.R-project.org/package=ClinicalRobustPriors, developed by one of the authors, which can be used to compute probabilities and figures for the prior, likelihood and posterior models.

The posterior mean in the normal/normal model is $(n_0\mu + n\overline{X}_n)/(n_0 + n) = -0.77$ with standard deviation $\sigma/\sqrt{n_0 + n} = 0.25$; the estimated odds ratio is $e^{-0.77} = 0.46$ or 54% risk reduction.

In the Cauchy/normal and intrinsic/normal, models the posterior mean is -1.48 ($e^{-1.48} = 0.22$ or 78% risk reduction) with standard deviation 0.32. In the normal/normal an 95% credible interval on the $\log(OR)$ scale is between -1.27 and -0.28, that corresponds to odds ratios from 0.28 to 0.75, or a 95% probability that the true risk reduction lies between 25% and 72%. For the Cauchy/normal and intrinsic/normal posterior models, the 95% credible interval shows that the true risk reduction lies between 57% and 88%. The likelihood shows a risk reduction between 60% and 90%.

In Figure 1 we can see that the normal skeptical prior is more dogmatic than both the Cauchy and intrinsic skeptical priors. When there is a discrepancy be-

tween prior and data, the robust priors are discarded to some extent in favor of the likelihood, but the normal prior is not.

As a counterbalance to the skeptical priors, Spiegelhalter et al. (1994) suggest an "enthusiastic" (or "optimistic" as we call it here) prior centered on the alternative hypothesis and with a high chance that the true treatment benefit is over 50%. In this example, the alternative hypothesis is $\theta_H = -0.69$ (50% risk reduction) and the high chance is $1 - \xi = 0.975$. The scale and prior sample size are the same as with the skeptical priors. Figure 2 display the results. The posterior mean in the normal/normal conjugate model is -1.13 ($e^{-1.13} = 0.32$ or 68% risk reduction), much closer than the -1.39 ($e^{-1.39} = 0.24$ or 76% risk reduction) of the Cauchy/normal or intrinsic/normal models. The scale for the posterior models are 0.25 and 0.34, respectively, with normal and Cauchy (or intrinsic) priors. For the Optimistic prior, there is no strong conflict with the likelihood and the inference with normal and robust priors is similar.
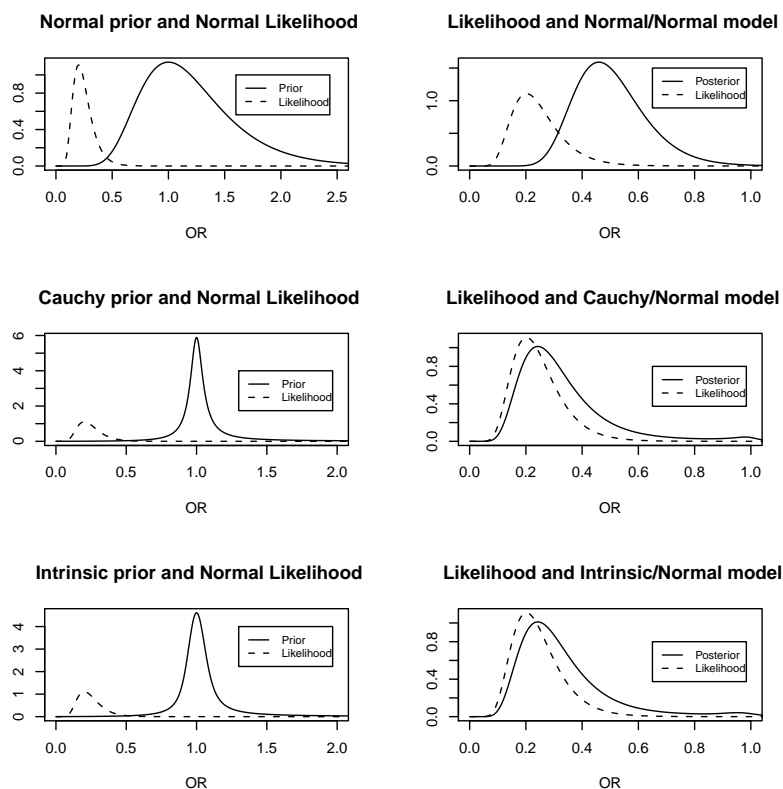

FIGURE 1: Skeptical priors, likelihoods and posterior models: normal/normal, cauchy/normal and intrinsic/normal.
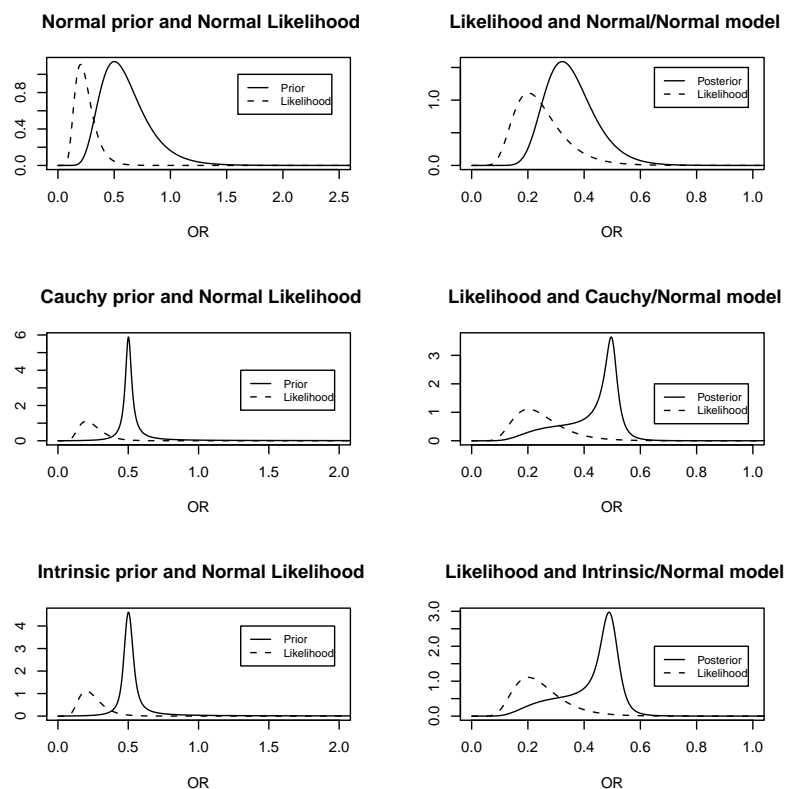
FIGURE 2: Optimistic priors, likelihoods and posterior models: normal/normal, cauchy/normal and intrinsic/normal.

Conclusion for the example. The quantity of interest is the set of a reduction of risk of at least of 50%, that is H_1. For the normal skeptical prior, the posterior probability can be calculated in the log-odds scale as $\Phi((-0.69 + 0.77)/0.25) = \Phi(0.32) = 0.62$. This contrast with both the Cauchy and intrinsic skeptical robust priors, for which this probability is 0.95. In other words, the hypothesis H_1 is supported by the data, even assuming the Cauchy and intrinsic skeptical robust priors. This is not the case with the normal skeptical prior. Next consider the optimistic priors case. This probability with the normal prior is $\Phi((0 + 1.13)/0.25) = \Phi(4.52) = 0.99$. The same probability is obtained with both the Cauchy and the intrinsic. Thus, in the example, the skeptical and optimistic robust priors have converged in over 95% of probability of the region of substantial improvement. Unfortunately, using the normal priors, the procedure has not yet converged, and much more evidence is still required for a definitive conclusion, and this is due entirely to the particular functional form chosen for the prior, and not to its condition of skepticism. In our experience, the results obtained by using any of the considered robust priors, Cauchy or intrinsic or Berger's prior, yield essentially the same results.

In next section, we demonstrated the behavior observed in the illustration is a general feature of robust and normal priors, rather than specific phenomenon of this example.

3. Asymptotic Results

In this section we show that robust priors can "change their mind" more readily than conjugate priors by looking at asymptotic properties of posterior means under each type of prior. When both the skeptical and optimistic prior are robust, they may reach agreement more quickly than if the two priors were not robust.

Consider a single sample y from a normal(θ, σ^2) distribution where θ has a conjugate normal$(0, \tau^2)$ prior. It is well-known that the posterior distribution on θ has mean

$$\frac{\tau^2}{\tau^2 + \sigma^2}y.$$

If we use a Cauchy$(0, 1)$ prior rather than a normal$(0, \tau^2)$ prior on θ above, the posterior mean of θ is

$$y - \mathcal{O}\left(\frac{1}{y}\right)$$

as $y \to \infty$. See the technical report Cook (2010) for the derivation of this asymptotic result.

Under the normal prior, the posterior mean of θ under-estimates the data y by a constant ratio that depends on the relative scales of the sampling distribution and the prior distribution. Under the Cauchy prior, however, the posterior mean of θ asymptotically approaches the value of y, independent of the scales of the sampling and prior distributions. This is illustrated by Figure 3.

Next we consider the case of n samples y_i with mean $\overline{y}$ and consider $n \to \infty$ the behavior of the posterior mean. Under a normal$(0, \tau^2)$ prior, the posterior mean is given by

$$\frac{1}{1 + \frac{\sigma^2}{n\tau^2}}\overline{y} = \left(1 - \frac{\sigma^2}{n\tau^2} + \mathcal{O}\left(\frac{1}{n^2}\right)\right)\overline{y}$$

Under a Cauchy prior, however, the posterior mean is

$$\overline{y} + \frac{(\overline{y}^2 - 3)\overline{y}}{(1 + \overline{y}^2)^2}\frac{\sigma^2}{n} + \mathcal{O}\left(\frac{1}{n^2}\right)$$

The rate at which the posterior mean converges to $\overline{y}$ depends on τ in the case of the normal prior and on $\overline{y}$ in the case of the Cauchy prior. For any value of τ, the convergence is faster under the Cauchy prior for sufficiently large values of $\overline{y}$.

We now obtain results for Berger's prior that are quite similar to those above for the Cauchy prior. If we observe n samples from a normal(θ, σ^2) distribution
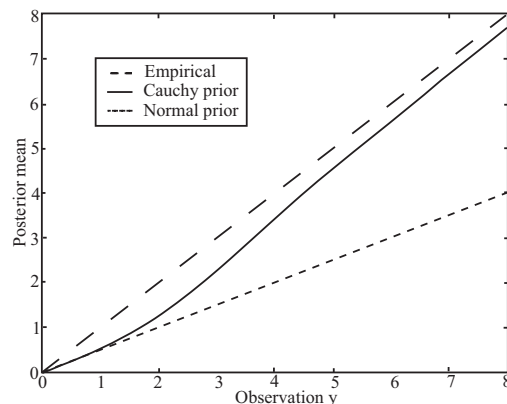
FIGURE 3: Posterior mean of θ under robust and conjugate priors compared to empirical value.

and θ has Berger's prior with location 0, the posterior mean of θ is

$$\frac{2\sigma^2\overline{y}}{(\sigma^2 + n\beta^2)\left(\exp\left(\frac{n\overline{y}}{\sigma^2+n\beta^2}\right) - 1\right)} - \frac{2\sigma^2}{n\overline{y}}$$

where $\overline{y}$ is the sample mean of the observations as shown in Fúquene et al. (2009). Therefore as a single sample $y \to \infty$, the posterior mean of θ is

$$y - \frac{2\sigma^2}{y} + \mathcal{O}(\exp(-y^2))$$

Also, as $n \to \infty$, the posterior mean of θ is

$$\overline{y} - \frac{\sigma^2}{n}\frac{2}{\overline{y}} + \mathcal{O}(\exp(-n))$$

These results show that, for Cauchy and Berger priors, the influence of the prior diminishes more quickly when the data are far from the location parameter of the prior. When skeptical and optimistic priors using either of these robust distributions, the priors will reach consensus more quickly than corresponding conjugate priors when the data are in conflict with one of the priors.

4. Conclusions

The idea of skeptical and optimistic priors is an important one, and useful to increase the impact of Bayesian statistics in the whole of medical statistics. As introduced by Spiegelhalter et al. (2004), this idea has two components. The first is that the prior probability of the region where the new treatment is substantially better than the current treatment is high for the optimistic prior and low for the skeptical prior. The second component is the specific shape of the priors

(effectively a class of two priors), that was assumed normal priors by Spiegelhalter et al. (2004). We show here, to the best of our knowledge for the first time, that the behavior of the procedure, even complying with the first component, crucially depends on the shape of the priors, particularly the tail size. We illustrate that with an example, similar as those in Spiegelhalter et al. (except that the equivalent sample sizes of the likelihood and priors are about the same in our example) and show it mathematically in Section 3. Furthermore, we put forward that the idea of skeptical and optimistic prior is actually improved by the use of heavy tailed priors, because the procedure is "less stubborn" and even though it places a handicap on both hypothesis, it is more willing to change its mind when there is clear information in favor of one of the hypothesis. As a consequence, the robust procedure put forward here is able to embrace better treatments or to discard bad ones in a more efficient manner: it is more likely that the optimistic and skeptical procedure reach a consensus under robust heavy tailed priors than under normal priors. Finally, the use of different heavy tailed priors presented here, the Cauchy, Berger's or Intrinsic priors lead to essentially equivalent statistical behavior, and thus the choice among them is more a matter of convenience and taste. But the difference between normal and robust skeptical/optimistic priors is substantial, and the robust version of the idea seems to us much more acceptable for the players involved.

Acknowledgements

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Appendix

A1. Resumen

Los ensayos clínicos son contenciosos y controversiales. Las compañías farmacéuticas están ansiosas de probar que el tratamiento nuevo, en el que han invertido fortunas, es una mejora sustancial sobre el tratamiento actual. Por el contrario, las agencias reguladoras gubernamentales adoptan la posición contraria y exigen, por evidencia inequívoca, que el nuevo tratamiento sea sustancialmente mejor que el actual.

La estadística bayesiana permite emplear una técnica muy útil para modelar posiciones encontradas, usando no una sino dos distribuciones *a priori* sobre los parámetros. Una es la previa optimista, que corresponde a la expectativa favorable. La otra, la previa pesimista, que corresponde a una posición escéptica.

Para ser mas específicos, consideremos el siguiente test unilateral. Supongamos que tenemos dos tratamientos médicos que corresponden a probabilidades de eventos p_1 y p_2. Los eventos pueden ser, por ejemplo, "recurrencia del evento" o "muerte". La Tasa de Chances (Odds Ratio) está definida como

$$OR = \frac{p_1/(1-p_1)}{p_2/(1-p_2)}$$

y para hacer el supuesto de normalidad más realista consideramos los log odds: $\theta = \log(OR)$. Con frecuencia, el test de interés es

$$H_0 : \theta \geq \theta_H, \ vs \ H_1 : \theta < \theta_H \tag{5}$$

Acá, H_1 es la región de mejoría sustancial del nuevo tratamiento sobre el standard. Entonces, $\theta_H < 0$, corresponde a $OR < 1$; por ejemplo, $OR = 0{,}5$ es el punto de 50 % de mejoría.

La primera parte de la propuesta de Spiegelhalter et al. (2004) es suponer dos densidades *a priori*, π_S and π_O (escéptica y optimista respectivamente), que

cumplan con las siguientes especificaciones. La escéptica se centra en el punto de no diferencia, es decir, en $\theta = 0$, y le da una probabilidad pequeña, denotada por ξ, digamos $\xi = 0{,}05$ o $\xi = 0{,}025$, a la hipótesis alternativa de mejoría sustancial, es decir a H_1, esto es:

$$P_S(H_1) = \int_{-\infty}^{\theta_H} \pi_S(\theta) d\theta = \xi \tag{6}$$

Por otro lado, la previa optimista esta centrada en θ_H y le da probabilidad ξ, de que no hay beneficio con el tratamiento nuevo, y entonces

$$P_O(\theta > 0) = \int_{0}^{\infty} \pi_0(\theta) d\theta = \xi \tag{7}$$

Si bajo la previa escéptica, $P(H_1 \mid \text{datos}, \pi_S) > 1 - \gamma$, con $1 - \gamma$ grande, digamos $1 - \gamma = 0{,}95$, entonces, habiendo convencido a un escéptico es seguro decidir en favor de H_1. Si por el contrario, con la previa optimista $P_O(\theta > 0 \mid \text{datos}) > 1 - \gamma$, es seguro concluir que no hay beneficio con el tratamiento nuevo. Si hay desacuerdo entre los procedimientos, el ensayo no es inconcluyente dada la información acumulada hasta el momento.

Este enfoque es intuitivamente muy satisfactorio. Sin embargo, tiene el defecto potencial de ser demasiado cauteloso y conservador, dilatando innecesariamente las decisiones. En Spiegelhalter et al. (2004) se proponen previas normales, las cuales simplifican las cuentas. Sin embargo, en este artículo mostramos que podemos preservar las ventajas del enfoque optimista vs. escéptico, pero eliminando el dogmatismo inherente en las previas conjugadas (normales en este caso).

Algunos antedecedentes. Pericchi & Smith (1992) estudiaron algunos aspectos de la robustez de la previa Student-t y un parámetro de localización normal, y proveyeron de aproximaciones los momentos de la densidad posterior bajo el modelo Student-t/normal. La previa Cauchy, como Student-t con un grado de libertad, puede ser utilizada en este contexto. También para normal "log-odds" (el parámetro θ definido arriba) existe una previa definida por Berger (1985), que además de tener colas pesadas, da resultados que pueden ser calculados en forma cerrada, esto es, con expresiones matemáticas concretas en lugar de resultados numéricos. Otra previa de colas pesadas ha sido propuesta por Berger & Pericchi (1996); la llamada previa intrínseca. Todas estas previas de colas pesadas dan resultados prácticamente idénticos, hecho ilustrado por Fúquene et al. (2009). En este último artículo, se estudian previas robustas, basadas en resultados de ensayos clínicos previos: las así llamadas previas clínicas. Las previas estudiadas en el presente artículo modelizan no historia previa, sino posiciones adversas frente a un ensayo clínico nuevo; las previas escépticas vs optimistas. En este trabajo ilustramos que suponiendo estas previas, respetando los requerimientos probabilísticos de Spiegelhalter et al. (1994), pero cambiando su forma funcional a previas robustas, obtenemos ensayos clínicos más eficientes en los que se produce la convergencia de criterios en forma más rápida y eficiente.

A2. Conclusiones

La idea de una previa escéptica vs. otra previa optimista es muy útil para incrementar la utilización de la estadística bayesiana en la estadística médica. Esta idea introducida por Spiegelhalter y colaboradores, tiene dos aspectos: el primero es que la región donde el tratamiento nuevo es sustancialmente mejor tiene alta probabilidad bajo la previa optimista y baja probabilidad bajo la previa escéptica. El segundo aspecto es la forma funcional de las dos previas. Eso fue supuesto por Spiegelhalter et al. (1994) como previas normales. Se muestra acá, lo inédito, que el comportamiento del procedimiento depende crucialmente de la forma funcional de las previas optimistas y escépticas, particularmente del tamaño de las colas. Lo ilustramos con un ejemplo en la sección 2 y lo demostramos matemáticamente en la sección 3. Más aún, se sostiene que el comportamiento con colas gruesas mejora y hace más eficiente el procedimiento, ya que las previas con colas gruesas están mas dispuestas a cambiar de opinión que las previas de colas finas. Finalmente, el uso de la previa de Cauchy, de Berger o Intrínseca resultados análogos para efectos prácticos.

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