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Contents

A fully Bayesian approach for sample size determination of Poisson clinical trials.

Approccio completamente Bayesiano per la scelta della dimensione campionaria di studi clinici basati su dati di conteggio.

Susanna Gentile and Valeria Sambucini

Abstract In this paper, we exploit a fully Bayesian approach to determine the optimal exact sample size of a single-arm trial based on count data. The idea is to select the sample size by controlling the *Predictive Bayesian Power*, i.e. the predictive probability of obtaining a Bayesian significant result, under the assumption that the treatment is actually effective. An essential element of the procedure is the specification of two different prior distributions and some suggestions about their choice are provided.

Abstract *In questo articolo si sfrutta un approccio completamente bayesiano per la scelta della numerosità campionaria esatta per uno studio a braccio singolo basato su dati di conteggio. L'idea è di selezionare la dimensione del campione controllando la Potenza Bayesiana Predittiva, ovvero la probabilità predittiva di ottenere un risultato statisticamente significativo secondo un ottica Bayesiana, assumendo che il trattamento sia effettivamente efficace. Un elemento essenziale della procedura è l'introduzione di due diverse distribuzioni a priori sulla scelta delle quali vengono forniti alcuni suggerimenti.*

Key words: Exact sample size determination, fully Bayesian approach, Poisson data, Predictive Bayesian Power, two-priors approach.

Susanna Gentile
Dipartimento di Scienze Statistiche, Sapienza Università di Roma
e-mail: gentile.1705895@studenti.uniroma1.it

Valeria Sambucini
Dipartimento di Scienze Statistiche, Sapienza Università di Roma
e-mail: valeria.sambucini@uniroma1.it

1 Introduction

The choice of the sample size is a key element of any study design, especially in the field of clinical trials. In this context, Bayesian methods for sample size calculation are particularly attractive because of their flexibility and capability of modelling uncertainty. In this paper, we adopt a "fully Bayesian approach", also called a "proper Bayesian approach", that does not mix frequentist and Bayesian tools, but uses only Bayesian concepts both at the analysis and at the design stage of the trial. As a consequence, the method requires the specification of two different prior distributions, which pursue different purposes: the *analysis* and the *design* priors (see [1], [3] and [7]).

Let us focus on hypothesis testing and consider the null hypothesis $H_0 : \theta \in \Theta_0$ versus the alternative $H_1 : \theta \in \Theta_1$, where θ denotes the parameter of interest that measures the effect of the experimental treatment. The hypothesis H_1 defines the condition about the parameter that corresponds to a treatment considered sufficiently effective. In a Bayesian setup, we elicit the analysis prior distribution, $\pi^A(\theta)$, that expresses the pre-experimental knowledge, as well as the possible absence of information, about the unknown parameter θ. It is used to compute the posterior distribution, $\pi^A(\theta|y_n)$, where y_n denotes the observed experimental result based on a sample of size n. At the planning stage of the trial, we have not collected the trial data yet and the experimental result is a random quantity, Y_n. Following Spiegelhalter et al. [6], this random result can be considered statistically significant under a Bayesian perspective if it yields a large posterior probability that θ belongs to the alternative hypothesis. In other words, the definition of the *Bayesian significance* provides the condition to obtain a successful experiment that leads to the rejection of the null hypothesis. The sample size determination criterion is based on the computation of the so-called *Predictive Bayesian Power*, $PBP(n)$, that is the predictive probability of obtaining a Bayesian significant result, when the true θ actually belongs to the alternative hypothesis. This latter optimistic assumption is realized by introducing a design prior distribution, $\pi^D(\theta)$, that assigns negligible probability values to the sub-space under H_0 and that is used to compute the prior predictive distribution of Y_n. In general terms, the criterion selects the minimum n that ensures a sufficiently large value for the Predictive Bayesian Power.

In this paper, we apply the fully Bayesian procedure described above for exact sample size calculation in single-arm trials based on count data. As a consequence of using exact methods, we obtain that $PBP(n)$ is not a monotonically increasing function of n, but tends to increase following a saw-toothed behaviour that typically occurs when dealing with discrete distributions of Y_n (see [2]). To take into account this behaviour, in line with Sambucini [5], we suggest to select the optimal sample size as

$$n^{PBP} = \min\{n^* \in \mathbb{N} : PBP(n) > \gamma, \forall n \geq n^*\}, \tag{1}$$

where γ is a fixed threshold. In practice, this more conservative criterion takes into account the behaviour of $PBP(n)$ by imposing that the condition of interest is satisfied for all the sample size values greater than or equal to the optimal one.

The outline of the article is as follows. In Section 2, we illustrate the Bayesian formulation of the problem when a single-arm study with Poisson data is performed and describe the sample size determination criterion based on $PBP(n)$. In Section 3 we show some numerical results and provide some suggestions about the choice of the analysis and the design priors. Finally, Section 4 contains some concluding remarks.

2 Sample size determination based on $PBP(n)$ for Poisson data

Let $(X_1, X_2, ..., X_n)$ be a random sample of count data. We assume that, for $i = 1, ..., n$, X_i represents the number of negative events occurred over a period of time for the i-th patient enrolled in a single-arm study aimed at establishing the efficacy of a new experimental treatment. Each X_i follows a Poisson distribution of rate $\theta > 0$, so that the sampling distribution of the sufficient statistic $S_n = \sum_{i=1}^{n} X_i$ is $f(s_n|\theta) = \text{pois}(s_n; n\theta)$, for $s_n = 0, 1, 2, \cdots$. The experimental treatment can be considered sufficiently effective if the event rate is below a target value θ_0 and, therefore, the interest is focused on the hypotheses $H_0 : \theta \geq \theta_0$ and $H_1 : \theta < \theta_0$.

Under a Bayesian framework, we exploit standard conjugate results and introduce a *gamma analysis prior distribution* to account for pre-experimental information on θ, $\pi^A(\theta) = \text{gamma}\left(\theta; \alpha^A, \beta^A\right)$, with $\alpha^A, \beta^A > 0$. The corresponding posterior distribution is $\pi^A(\theta|s_n) = \text{gamma}\left(\theta; \alpha^A + s_n, \beta^A + n\right)$. At the planning stage of the trial, the *Bayesian significance* of the random result S_n is provided by the condition

$$\mathbb{P}_{\pi^A(\cdot|S_n)}(\theta < \theta_0) = \text{Gamma}(\theta_0; \alpha^A + S_n, \beta^A + n) > \lambda, \tag{2}$$

where λ is a fixed probability threshold, $\mathbb{P}_{\pi^A(\cdot|S_n)}$ denotes the probability measure associated with the posterior distribution of θ and $\text{Gamma}(\cdot; a, b)$ denotes the c.d.f. of a gamma distribution of parameters a and b. The posterior probability in (2) is a decreasing function of S_n and, due to the discreteness of the random result, it is possible to find a non-negative integer k such that

$$\mathbb{P}_{\pi^A(\cdot|k)}(\theta < \theta_0) > \lambda \qquad \text{and} \qquad \mathbb{P}_{\pi^A(\cdot|k+1)}(\theta < \theta_0) \leq \lambda.$$

As a consequence, we can say that the random result S_n is significant under a Bayesian perspective if $S_n \leq k$, where

$$k = \max\left\{u \in \{0, 1, \cdots\} : \text{Gamma}\left(\theta_0; \alpha^A + u, \beta^A + n\right) > \lambda\right\}.$$

In order to derive the Predictive Bayesian Power, we introduce a *gamma design prior distribution*, $\pi^D(\theta) = \text{gamma}\left(\theta; \alpha^D, \beta^D\right)$, with $\alpha^D, \beta^D > 0$, used to

formalize the optimistic design expectations about the efficacy of the experimental treatment. By exploiting this prior density, we obtain the following Negative-Binomial prior predictive distribution of S_n

$$m^D(s_n) = \text{Nb}\left(s_n; \alpha^D, \frac{\beta^D}{\beta^D + n}\right), \quad \text{for } s_n = 0, 1, 2, \cdots.$$

Then, the Predictive Bayesian Power can be obtained as

$$\begin{aligned} PBP(n) &= \mathbb{P}_{m^D(\cdot)}(S_n \leq k) \\ &= \sum_{s_n=0}^{k} \text{Nb}\left(s_n; \alpha^D, \frac{\beta^D}{\beta^D + n}\right), \end{aligned}$$

where $\mathbb{P}_{m^D(\cdot)}$ denotes the probability measure associated with the prior predictive distribution of S_n. In practice, it is given by the sum of the predictive probabilities of all the possible Bayesian significant results, obtained under the assumption that the experimental treatment is actually effective. Given the discrete nature of the Negative-Binomial distribution, we propose to use the conservative criterion in (1) to select the optimal value of n.

3 Numerical results

In this Section, we analyse the impact of the different design parameters on the optimal sample size. Let us assume that $\theta_0 = 1.9$. To elicit the gamma design prior, we find it useful to follow a procedure commonly used for the beta prior densities in the presence of binary data, that consists in expressing the hyperparameters in terms of prior mode and prior sample size (see [4]). In our case, we obtain that by setting

$$\alpha^D = n^D \theta^D + 1 \qquad \text{and} \qquad \beta^D = n^D,$$

$\pi^D(\theta)$ is centred on θ^D and its concentration can be regulated by varying the prior sample size n^D. Since we use this distribution to assume that θ belongs to the alternative hypothesis, it is reasonable to fix θ^D smaller than θ_0 and to set n^D so that the prior probability assigned to the null hypothesis is negligible. In particular, we consider two possible strategies to select n^D: (i) we set $n^D = \infty$, obtaining that $\pi^D(\theta)$ assigns all the probability mass to θ^D and (ii) we select n^D as the smallest value such that $P(\theta < \theta_0) \simeq 0.999$. Note that, in the first case, no uncertainty is introduced at the planning stage and the Predictive Bayesian Power equals the so-called *Conditional Bayesian Power* (see [1] and [5]). For the analysis prior, we similarly ensure that the prior mode is θ^A, but we set the prior sample size n^A equal to 1, in order to represent weak prior information that lets the data be predominant in the posterior analysis.

In Figure 1, we show the behaviour of $PBP(n)$, when $\theta^D = 1.5$, $\theta^A = 1.9$ and $\lambda = 0.95$. Because of the saw-toothed shape, we fix $\gamma = 0.8$ and select the optimal

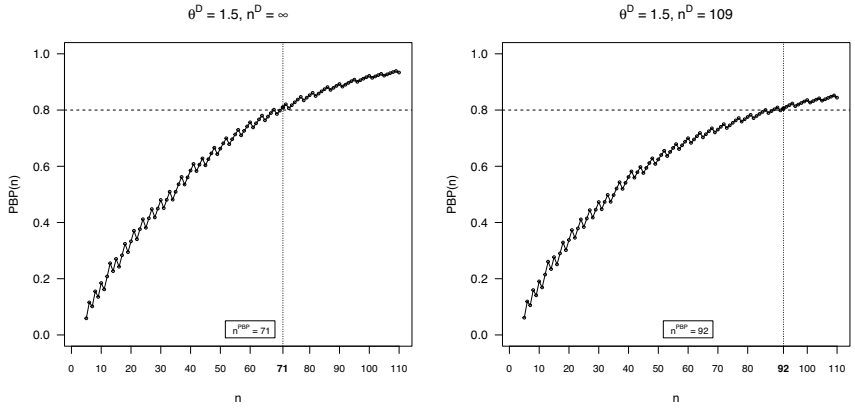

Fig. 1 Behaviour of $PBP(n)$, when $\theta_0 = 1.9$, $\theta^A = 1.9$, $n^A = 1$ and $\lambda = 0.95$. The optimal sample size is selected according to the criterion in (1) for $\gamma = 0.8$.

sample size according to the criterion in (1). We can note that, when $n^D = \infty$ and no uncertainty is accounted for through the design prior, the Bayesian power increases faster and the corresponding n^{PBP} is smaller. The same behaviour can be observed in Table 1, which reports the optimal sample sizes for $\gamma = 0.8$ for different values of θ^A, θ^D, λ and n^D. More specifically, the gap between the two sample sizes increases as θ^D gets closer to θ_0. Regardless of n^D, the selection of θ^D especially impacts the optimal sample sizes because we are considering three completely different scenarios under H_1. In particular, the closer θ^D and θ_0 are, the larger n^{PBP} is. The sample size also increases with λ because we require stronger evidence to consider the result statistically significant. Finally, even though the analysis priors are weakly informative, the optimal sample size increases with the degree of prior scepticism towards the new treatment expressed by $\pi^A(\theta)$. In this case, given the hypothesis system at interest, a larger θ^A expresses stronger scepticism.

4 Conclusion

In the present paper, we address the problem of sample size determination for single-arm studies based on Poisson data. More specifically, we adopt a fully Bayesian approach by exploiting the concept of Predictive Bayesian Power. The proposed strategy has two important advantages in that (i) it allows the introduction of possible pre-experimental knowledge about θ through the specification of an analysis prior distribution and (ii) it models uncertainty on θ at the planning stage with the design prior distribution, avoiding local optimality. Moreover, instead of using normal approximations, we resort to exact methods based on discrete

Table 1 Optimal sample sizes for different values of θ^D, n^D, θ^A and λ, when $\theta_0 = 1.9$, $n^A = 1$ and $\gamma = 0.8$.

		$\lambda = 0.9$			$\lambda = 0.95$			$\lambda = 0.99$		
		θ^A			θ^A			θ^A		
θ^D	n^D	0.9	1.9	2.9	0.9	1.9	2.9	0.9	1.9	2.9
1.5	∞	48	52	57	66	71	75	109	113	118
	109	58	66	71	84	92	97	143	151	156
1.6	∞	86	95	101	121	126	132	196	205	210
	195	107	117	123	152	162	168	260	270	279
1.7	∞	200	212	219	280	287	298	453	464	475
	444	249	262	270	353	366	374	600	612	625

distributions of the data and a conservative criterion is necessary to account for the not monotonic behaviour of $PBP(n)$.

Finally, let us notice that, without loss in generality, we have considered the count of "negative" events, that represent a not-desired outcome for patients. The proposed Bayesian criteria can be similarly derived when the hypotheses are reversed because a "positive" event is considered.

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