Potential of the Bayesian approach in critical care

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Abstract

Bayesian statistics are becoming increasingly popular in medical data analysis and decision-making. Because of the difficulties that RCTs face in critical care, these methods may be particularly useful. We explain the fundamental concepts and examine recent relevant literature in the field.

Introduction

The frequentist approach to statistical inference, which is widely employed in medical literature and affects clinical practice,[1] is predicated upon only making predictions on the reality underlying an experiment with data gleaned from the experiment itself, which will determine if the null hypothesis will be able to be rejected in favor of the one being tested.

There are some issues in the usage of strictly frequentist criteria in the analysis of the results of a clinical trial, connected to the assumption that there are no differences between the control group and the treatment group: it's hard to test multiple hypotheses, interpreting the results to establish clinical benefit is complex and already known information cannot be taken into account.[2]

Bayes' theorem

Bayes' theorem, which can be derived from the definition of conditional probability, can in its simplest form be stated as:

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

Where *P(A)* and *P(B)* are *a priori* probabilities (meaning that they do not change due to other information), *P(A|B)* and *P(B|A)* are *conditional* probabilities.

A clinical example

A 44-year-old man, having been feverish for days, vomited food and experienced a rapid deterioration of his level of consciousness on the day of access to the ER. On admission, the patient responds to pain stimulus, is feverish (39°C), GCS 11 E2V4M5, with no focal neurological signs. The medical history is silent.

Clinical observation suggests an unknown infection (herpes encephalitis is suspected after blood count and biochemistry tests, and a spinal tap is performed) in an advanced stage; in this scenario, fluid resuscitation and antiviral therapy might be lifesaving; the same wouldn't be true for an older patient, with acute abdomen and aortic dissection. This kind of inductive reasoning is employed daily to make clinical decisions, updating the diagnostic hypotheses in light of the availability of new data; in other words, the probability that the diagnostic hypothesis is true is conditioned by new evidence:

$$P(Encephalitis|Clinical\ data) = \frac{P(Clinical\ data|Encephalitis)P(Encephalitis)}{P(Clinical\ data)}$$

Where *P(Clinical data)* is the a priori probability for the patient to present the observed symptoms and anamnesis (which can be estimated by experts from their experience or in some cases calculated by summation of the prevalences of all the compatible diagnostic hypotheses) and *P(Encephalitis)* is the prevalence of the disease in the relevant population (which can be derived from studies on the topic); at each stage of the process (medical history, preliminary examination, blood tests, spinal tap) the hypothesis is re-evaluated and grows more plausible: i) before the spinal tap, the pre-test odds might be 10:1 (≈91%) for infection, 2.5:1 (≈40%) for meningitis or encephalitis; ii) given a sensitivity and specificity of 95% of PCR tests of cerebrospinal fluid for viral encephalitis,[3] the positive likelihood ratio is 19, the negative 0.05; iii) the post-test odds are 47.5:1 (≈98%) for viral encephalitis.

It's important to note how the post-test odds for any step in the diagnostic path can become the pre-test odds for the following one.

Interpretations of Bayes' theorem

From a frequentist viewpoint, the concern is the probability of a certain set of data, while in the Bayesian approach, the subject of probability is the hypothesis.[4]

Bayes' theorem, by itself, is only a mathematical statement that is compatible with a frequentist approach; in frequentist statistics, it can be seen as describing the outcomes of a repeated experiment: *P(A)* is the proportion of runs that exhibits the A property, *P(B)* the proportion of runs that exhibits the B property and *P(A|B)* is the proportion of the subset of A-property runs among the B-property runs.

In Bayesian statistics, however, the theorem is a tool to account for the effect of new evidence on belief: *P(A)* is the *prior*, quantifying the initial strength of belief in A, *P(A|B)* is the *posterior*, quantifying the belief in A with the newly emerged truth of B taken into account.

Finding Bayesian priors

It is typical of human cognition to continuously make inferences regarding the surrounding reality, as it is for a physician in daily clinical practice (as in the example discussed before), where priors can come from various sources: the prevalence of a disease derived from epidemiological data, randomized controlled trials, meta-analyses, the individual patient's medical history.

The interpretation of these sources isn't necessarily identical even between different experts, but it is possible to build a prior distribution by formalizing and mathematically processing the degree of belief among a number of them or, failing that, using non-informative priors (which means using no related data to calculate the first posterior distribution).[5]

Bayesian statistic in clinical trials

The number of published studies using Bayesian methods has significantly increased in recent years.[6]

Grant *et al.*[7] find that a single lesson in Bayesian statistics (focused on the evaluation of medical tests) significantly improves the ability of critical care resident physicians to interpret results, as conventional approaches focused only on sensitivity and specificity may fail to convey how impactful a test is on the likelihood of disease (the magnitude of the effect of the test on such a likelihood is explicit in Bayesian statistics).

Numerous recent publications find advantages in the Bayesian approach, for example Neckebroek *et al.*[8] contrast three protocols for post-operative sedation (manual, predictive automatic, and Bayesian rule optimizer automatic) and conclude that the Bayesian protocol leads to satisfactory results while needing lower effector site remifentanil concentration than the other competitors. Yarnell *et al.*[2] re-examine 82 clinical trials whose results were originally evaluated using a frequentist approach with Bayesian methods. They find that in most cases the two approaches lead to the same conclusions, but they identify results that were found to be not statistically significant that still probably lead to clinical benefits and, conversely, significant results that were unlikely to confer clinical benefits. In several studies, the probability of clinical benefit was heavily dependent on the choice of Bayesian priors, which implies that not enough information was available to evaluate the effectiveness of the treatment.

Numerous sepsis trials have failed to translate to clinical benefits[9] and it has been argued[10] that the reliance on frequentist analysis is part of the issue due to the constraints imposed on trial design and the use of already available evidence, while the Bayesian approach would be better suited to the highly nonlinear system being studied. Tomlinson *et al.*[11] simulate conducting a sepsis treatment trial and conclude that the inclusion of reasonable historical data increases the study's statistical power (the probability of detecting a statistically significant effect if it exists).

There are advantages to using Bayesian methods in meta-analyses Kwok and Lewis[12] find that Bayesian hierarchical modeling is a useful tool for comparative effectiveness and treatment research, while the historical issues of computational complexity have been rendered moot by technological progress. Kalil and Sun[13] re-assess low-dose steroid sepsis trials from three contradictory meta-analyses with traditional and Bayesian methods. They find that the Bayesian analysis of the data is consistent and shows no improvement in mortality rates from the treatment.

Conclusions

Critical care RCTs often suffer from small sample sizes and insufficient statistical power for structural reasons,[14] a situation that a Bayesian approach could help remediate.

A closer resemblance to ordinary clinical reasoning and outputs that are more immediately applicable and easier to understand and quantify[1] (*i.e.* probabilities instead of p-values and a better understanding of effect size) are other advantages of Bayesian analysis.

The historical issue of computational difficulty that plagued Bayesian statistics has been solved by new mathematical techniques developed in the second half of the 20th century[6] and by the ubiquitous availability of powerful computers.

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