Bayesian Clinical Trials

An introduction to the Beta-Binomial model

Background

For a phase IIA trial, suppose our goal is to evaluate the response rate π for a new drug by testing the hypotheses

$$H_0 : \pi \leq p_0 \quad H_1 : \pi \geq p_1$$

Suppose we set a maximum number of accrued patients N_{max}, and assume that the number of responses X among the current n patients follows a Binomial distribution with parameter π. The binomial likelihood is:

$$f\left(x|\pi, n\right) = \binom{n}{x} \pi^x \left(1-\pi\right)^{1-x}$$

Prior

We assume that the prior distribution of the response rate, π, follows a Beta distribution:

$$g(\pi) = Beta(c, d) = B(c, d)^{-1} \pi^{c-1} (1 - \pi)^{d-1}$$

The quantity $c/(c + d)$ gives the prior mean, while the magnitude of $c + d$ indicates how informative the prior is. The larger this sum, the more informative the prior and the stronger the belief it contains.

The conjugacy property

By the conjugacy of the beta prior and binomial likelihood, the posterior distribution of the response rate follows a beta distribution with parameters $c + x$ and $d + n - x$:

$$f(\pi|x, n, c, d) = \frac{f(x|\pi, n)\, g(\pi)}{\int_0^1 f(x|\pi, n)\, g(\pi)\, d\pi}$$

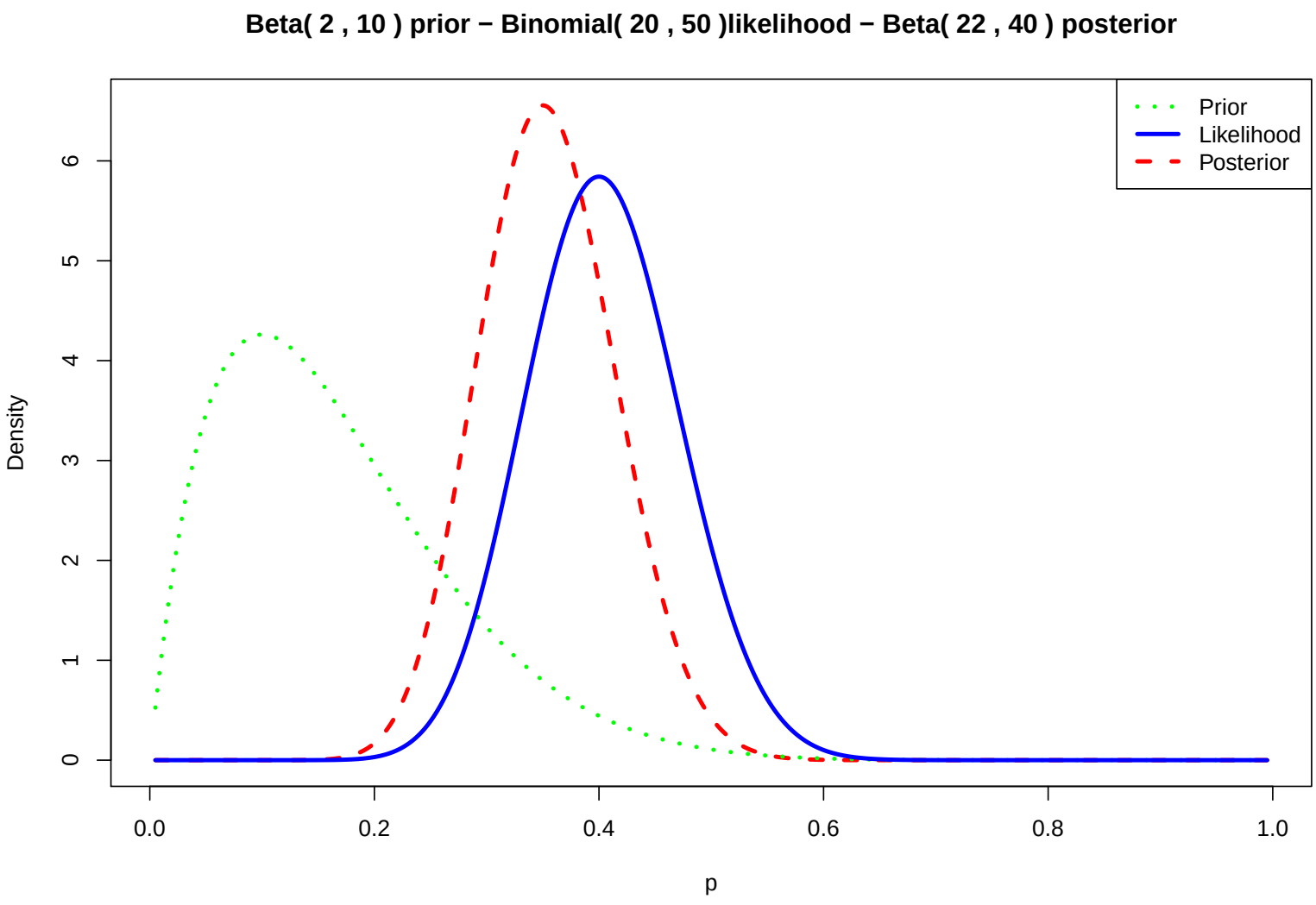
$$f(\pi|x, n, c, d) = \frac{\pi^{c+x-1}(1-\pi)^{d+n-x-1}}{B(c + x, d + n - x)}$$

Whenever we have a prior that is conjugate to the likelihood, the posterior distribution belongs to the same family of distributions as the prior. As a consequence, conjugate priors are extremely useful tools in Bayesian statistics, since they make things a lot more analytically tractable.

Posterior distribution

Once we have computed (or obtained an estimate of) the posterior, inference comes down merely to summarizing this distribution, since by Bayes' Rule the posterior summarizes everything we know about the model parameters in light of the data.

Example


Beta(2 , 10) prior − Binomial(20 , 50)likelihood − Beta(22 , 40) posterior
Prior
Likelihood
Posterior
Density
0
1
2
3
4
5
6
0.0
0.2
0.4
0.6
0.8
1.0
p

Posterior predictive probability

Suppose that you've constructed a beta-binomial model for data on the current n patients and you want to make a prediction about what you expect to happen next. The first thing that we might want to know is the posterior mean; that is, our best point estimate for π. This is given by:

$$E\left(\pi|x,n,c,d\right)=\int_0^1 \pi f\left(\pi|x,n\right)d\pi=\ldots=\left(c+x\right)/\left(c+d+n\right)$$

What about the more general prediction about future data?

Imagine that we then aim to enroll an additional m patients. What is the probability that exactly i of these are successes?

$$f\left(i|m,n,x,c,d\right)=\int_0^1 f\left(i|\pi,m\right)f\left(\pi|n,x,c,d\right)d\pi$$

The general name for the expected distribution over future observations is the posterior predictive distribution. If the prior distribution is $Beta\left(c,d\right)$ and the likelihood is $Binomial\left(n,\pi\right)$, then the posterior predictive distribution is a $Beta-Binomial\left(m,c+x,d+n-x\right)$ distribution.

The predictive probability approach looks into the future based on the current observed data to project whether a positive conclusion at the end of study is likely or not, and then makes a sensible decision at the present time accordingly.
Suppose that we can claim for efficacy is the posterior probability of π exceeding p_0 is greater than a threshold value γ. Let Y be the number of responses of m future patients following a $Beta - Binomial\,(m, c + x, d + n - x)$ distribution.
We can calculate the predictive probability (PP) of trial success as:

$$PP = \sum_{i=0}^{m} P\,(Y = i|\,x)\;\; I\,[P\,(\pi > p_0|x, Y = i) > \gamma]$$

A high PP means that the treatment is likely to be efficacious by the end of the study, given the current data, whereas a low PP suggests that the treatment may not have suffcient activity. We define a rule by introducing two thresholds on PP:

- if $PP < \gamma_{lower}$ then stop the trial and reject H_1
- if $PP > \gamma_{upper}$ then stop the trial and reject H_0
- otherwise continue accrual till reaching N_{max}

For phase IIA trials, we often prefer to choose $\gamma_{lower} > 0$ and $\gamma_{upper} = 1$ to allow early stopping due to futility, but not due to efficacy.

References

- Berry S.M., Carlin B.P., Lee J.J. , Muller P. Bayesian Adaptive Methods for Clinical Trials. 2011 Chapman & Hall.