Bayesian Designs for Early Drug Development Trials

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1702 - 1761

What is Probability?

The probability, p, of an event satisfies three axioms:

$$0 \le p(a) \le 1$$

$$p(a \text{ or } b) = p(a) + p(b)$$

$$p(a \text{ and } b) = p(a \mid b)\, p(b)$$

Bayes' Theorem for Simple Events

$$p(b \mid a) = \frac{p(a \mid b)\, p(b)}{p(a)}$$

Two Possible Interpretations of Probability

- Relative frequency (long-term average)
- Subjective degree of belief

Interpretations of Bayes Theorem

- Consider two hypotheses, H_0 and H_1
- Observe some data y relevant to the H_i
- Then:

$$p(H_0 \mid y) = \frac{p(y \mid H_0)\, p(H_0)}{p(y)}$$

$p(H_0)$ is the prior probability of H_0

$p(y \mid H_0)$ is the likelihood

$p(H_0 \mid y)$ is the posterior probability of H_0 given data y

Odds Form of Bayes' Theorem

$$\frac{p(H_0 \mid y)}{p(H_1 \mid y)} = \frac{p(y \mid H_0)}{p(y \mid H_1)} \frac{p(H_0)}{p(H_1)}$$

post odds = likelihood ratio x prior odds

likelihood ratio = 'Bayes factor'

Binomial Distribution

θ = probability of success in a single binary trial

y = number of successes in n independent trials

$p(\theta \mid y) \propto \theta^{y}(1-\theta)^{n-y}\, p(\theta)$

If $p(\theta) \propto \theta^{a-1}(1-\theta)^{b-1}$

then $p(\theta \mid y) \propto \theta^{a+y-1}(1-\theta)^{b+n-y-1}$

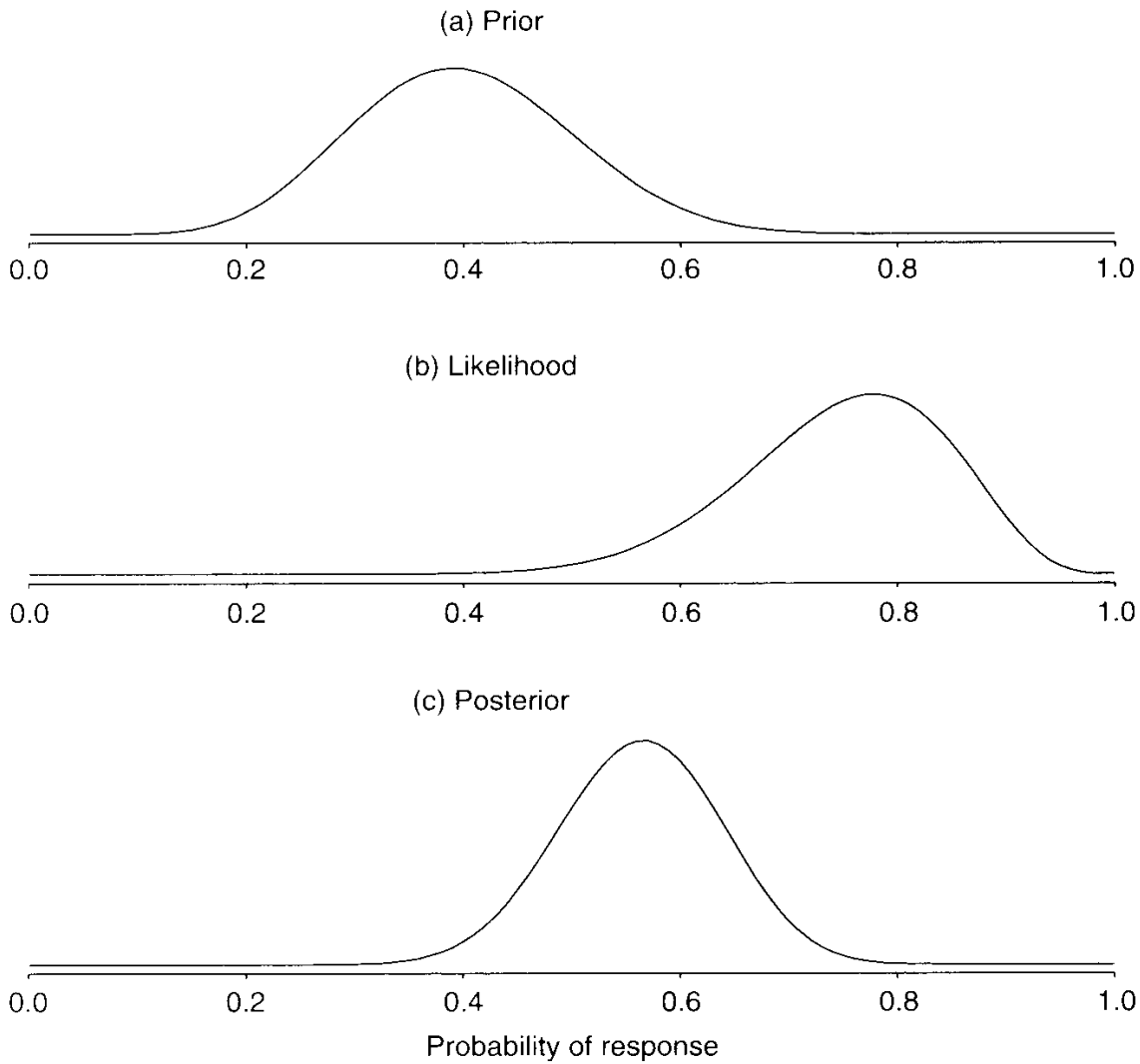
prior mean is $\dfrac{a}{a+b}$

posterior mean is $\dfrac{a+y}{a+b+n}$

Binomial Example

Spiegelhalter et al (2004), pages 60 - 61

- Prior: a = 9.2, b = 13.8
  - Mean: 9.2/23 = 0.40
  - 95% credible interval = [0.24, 0.64]
- Data: 15/20 = 0.75
  - 95% confidence interval = [0.51, 0.91]
- Posterior: a = 24.2, b = 18.8
  - Mean = 24.2/43 = 0.56
  - 95% credible interval = [0.43, 0.72]


(a) Prior
0.0
0.2
0.4
0.6
0.8
1.0
(b) Likelihood
0.0
0.2
0.4
0.6
0.8
1.0
(c) Posterior
0.0
0.2
0.4
0.6
0.8
1.0
Probability of response

Example (continued)

Hypothesis Testing

$H_0 : \theta \leq 0.50$

$H_1 : \theta > 0.50$

data: y = 15, n = 20, $\hat{\theta} = 0.75$

p-value (one-tailed) = 0.20

$p(\theta \leq 0.50) = 0.74$

$p(\theta \leq 0.50 \mid y = 15, n = 20) = 0.14$

Phase II Clinical Trials

Standard Statistical Approach

$$H_0: p \leq p_0$$
$$H_1: p \geq p_1$$

$$Pr\{\text{reject } H_0 \mid H_0 \text{ true}\} = \alpha$$
$$Pr\{\text{reject } H_1 \mid H_1 \text{ true}\} = \beta$$

Two-Stage Design

First stage (n_1 patients):

accept H_0 if $X_1 \leq a_1$

continue if $X_1 > a_1$

Second stage (additional n_2 patients):

accept H_0 if $X = X_1 + X_2 \leq a$

reject H_0 if $X > a$

n_1, n_2, a_1, a chosen to control error rates

CALGB 9332: Navalbine in SCLC

two-stage design

H_0: $p \leq 0.05$

H_1: $p \geq 0.20$

Pr {reject H_0 | H_0} = $\alpha = 0.10$

Pr {reject H_1 | H_1} = $\beta = 0.10$

$n_1 = 14$, $a_1 = 0$

n = 34, a = 4

CALGB 9332: Navalbine Results

stage 1 response rate = 2/14 = 0.14

overall response rate = 4/30 = 0.13

95% CI = (0.04,0.31)

P-value (one-sided) = 0.06

accept or reject H_0 ?

Bayesian Analysis of 9332

- Some possible priors (beta distribution):
  - Uniform (a = 1, b = 1)
  - Pessimistic (a = 1, b = 19)
  - Optimistic (a = 4, b = 16)
- Posterior distribution
  - Beta (a + y, b + n – y)

Bayesian Probabilities

Prior to Study

Prior	(a,b)	P ($\theta \leq 0.05$)	P($\theta \geq 0.20$)
Uniform	(1,1)	0.05	0.80
Pessimistic	(1,19)	0.62	0.01
Optimistic	(4,16)	0.01	0.45

Bayesian Probabilities

End of Stage 1 (data: 2/14 = 0.14)

Prior	(a+y,b+n-y)	P ($\theta \leq 0.05$)	P($\theta \geq 0.20$)
Uniform	(3,13)	0.04	0.40
Pessimistic	(3,31)	0.23	0.03
Optimistic	(6,28)	< 0.01	0.33

Bayesian Probabilities

End of Stage 2 (data: 4/30 = 0.13)

Prior	(a+y,b+n-y)	P ($\theta \leq 0.05$)	P($\theta \geq 0.20$)
Uniform	(5,27)	0.02	0.23
Pessimistic	(5,45)	0.10	0.02
Optimistic	(8,42)	< 0.01	0.21

Phase I Trials

Traditional 3 + 3 Design

- Define DLT
- Fix dose levels: d_0 , d_1 , d_2, …
- Three subjects at d_i
  - If 0 of 3 DLTs, escalate
  - If 1 of 3, add 3 subjects
    - If 1 of 6, escalate
    - If > 1 of 6, stop (MTD is d_{i-1})
  - If 2 of 3, stop (MTD is d_{i-1})

Phase I Clinical Trials

Bayesian Approaches

- Specify dose-toxicity model
- Set prior on parameters
- Enter cohorts, observe results
- Update probability distribution on parameters
- Select next dose based on predictive probability of toxicity distribution
- Stop when information is strong enough

Bayesian Designs for Phase I Trials

Thall and Lee 2003

- Continual reassessment method
- Logistic models

Advantages of Bayesian Designs Over 3 + 3 Design

- Higher probability of correct identification of MTD
- More patients treated at the correct MTD
- Fewer percentage of patients treated at doses exceeding the true MTD
- Less premature stopping

Advantages of a Bayesian Approach

- Intuitive and flexible procedures
- All evidence, internal and external, can be used
- Probability statements can be made about quantities of interest
- Focus is on how evidence changes beliefs
- Specification of prior requires careful discussion during design stage
- Recognition of the importance of context

Problems in Bayesian Approaches

- Unfamiliarity with Bayesian techniques
- Explicit use of subjective input
- Specification of priors
- Lack of standards in design, analysis, reporting
- Computational complexity
- Limited or unfriendly software