

A Study of Two Rival Methods in Calculating Bayesian Predictive Probability

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ABSTRACT

For oncology early phase single-arm studies there is a considerable increase in the popularity of applying Bayesian approaches to adaptively make decisions during the course of the trial. Bayesian predictive probability, computed as weighted average of posterior probabilities according to the currently observed data, just can be used to make Go or No-Go decisions for futility and efficacy. The intention of this paper is to make a comparison of the exact and stimulation algorithm in computing of predictive probability. The both algorithms are built in SAS and the codes are also provided in this paper. The exact algorithm involves in beta-binomial distribution for obtaining posterior probabilities. It's appropriate to employ the simulation algorithm – Markov Chain Monte Carlo (MCMC) to compute posterior probabilities when the Bayesian posterior distribution is not available in closed form. The paper found that both methods show fairly similar results in calculating of predictive probability. In other words, both methods are good fit on early phases data monitoring setting and which method to adopt only depends on the user's preferences.

INTRODUCTION

Interim efficacy monitoring plays a crucial role in most randomized trials especially in phase III. Group sequential design is usually used to evaluate whether to abort the trial early for efficacy. In phase II or earlier phase, however, there are fewer real time monitoring for efficacy providing much more evidence and continuous signals for phase III. Simon's two-stage design proposed by Simon (1989) [1] is often adopted to access if the trial will be terminated for futility from Frequentist perspectives but with some weaknesses, for example, it's hard to make decision when the number of subjects accrued is not fixed [2]. Bayesian predictive probability offers an extraordinarily distinct approach for continuous monitoring and adaptive decision-making. Predictive probability (PP) averages these posterior probabilities that hasn't been observed yet given the observed data and claims the experimental drug is either promising or not promising at the end of a study according to the accumulated data in the trial. There are two methods to obtain the predictive probability. One is the exact method, which is based on beta-binomial distribution to compute the posterior probabilities developed by Lee and Liu (2008) [3]. The other is the MCMC method used to compute posterior probabilities through drawing samples from a random posterior distribution assuming the Bayesian posterior distribution is not available in closed form [4-5].

THE EXACT ALGORITHM

Suppose a dose-expansion cohort with N subjects from a single-arm phase I trial and objective response rate (ORR), a binary variable, is regarded as the primary endpoint. Let p_E denote response rate for the experimental drug, N denote the maximum sample size and n be the number of treated subjects so far ($1 \leq n \leq N$). We assume Y is the number of responses among n treated subjects and follows a binomial distribution, $Y \sim \text{Bin}(n, p_E)$. We specify a non-informative beta prior distribution for p_E , $p_E \sim \text{Beta}(0.5, 0.5)$. If Y = y responses are observed among the n treated subjects, the posterior distribution of p_E will still follow a beta distribution on account of conjugation, $p_E | y \sim \text{Beta}(0.5 + y, 0.5 + n - y)$. We suppose X is the potential responses among (N - n) subjects enrolled in the future and follows a Beta-Bin distribution based on currently accumulated data y, $X | y \sim \text{Beta-Bin}(N - n, 0.5 + y, 0.5 + n - y)$. The probability mass function of this Beta-Bin distribution is shown as below, where B(.) denotes the Beta function:

$$\begin{aligned}
 P(x | y) &= \int_0^1 \binom{N-n}{x} p^x (1-p)^{N-n-x} \frac{p^{0.5+y-1} (1-p)^{0.5+n-y-1}}{B(0.5+y, 0.5+n-y)} dp \\
 &= \binom{N-n}{x} \frac{\int_0^1 p^{0.5+y+x-1} (1-p)^{0.5+N-y-x-1} dp}{B(0.5+y, 0.5+n-y)} \\
 &= \binom{N-n}{x} \frac{B(0.5+y+x, 0.5+N-y-x)}{B(0.5+y, 0.5+n-y)}
 \end{aligned}$$

Thus, the posterior distribution of p_E given current data y and potential data x of responses will be $p_E | (y, x) \sim \text{Beta}(0.5 + y + x, 0.5 + N - y - x)$. Let p_S denote standard response rate and θ_T be predefined target probability (θ_T). The experimental drug will be promising if the probability of $p_E > p_S$ given current data y and potential data x of responses is more than θ_T , $\text{Prob}(p_E > p_S | y, x) \geq \theta_T$. Because of the unknown x , we will average all probabilities based on future recruitment data to determine the predictive probability, where $I\{\cdot\}$ denotes the indicator function:

$$\text{Predictive Probability} = \sum_{x=0}^{N-n} P(x | y) I\{\text{Prob}(p_E > p_S | y, x) \geq \theta_T\}$$

The experimental drug can be considered effectiveness with a higher predictive probability at the end of the trial while futility with lower predictive probability. Let θ_U and θ_L be the probability threshold for efficacy and futility stopping respectively. If the predictive probability is more than θ_U , terminate the study and declare the experimental drug is promising. If the predictive probability is less than θ_L , terminate the study and declare the experimental drug is not promising. If the predictive probability is between θ_U and θ_L , continue to the next stage until the maximum sample size N .

The predictive probability can be obtained in Macro %**PPOS** according to the exact algorithm. Table 1 shows the results of calculating the predictive probability by Macro %**PPOS** ($N_{\text{max}} = 25$, $n = 15$, $Y = 8$, $P_s = 0.3$, $\theta_{t_t} = 0.9$, $a_0 = 0.5$, $b_0 = 0.5$, $\text{print} = \text{ALL}$), where the maximum sample size is 25 and 8 responses out of 15 treated subjects at interim analysis. In this case, the predictive probability is 0.92145. Let θ_U and θ_L be 0.8 and 0.2 respectively. Because the predictive probability is more than θ_U , the experimental drug would be regard as promising.

Table 1 Results of Calculating the Predictive Probability by the Exact Method

| X | P(x y) | $p_E (y, x) \sim \text{Beta}(0.5 + y + x, 0.5 + N - y - x)$ | | Prob($p_E > p_S y, x$) $p_S = 0.3$ | Indicator $\theta_T = 0.9$ | PP |
|----|----------|---|-----------------|---|-------------------------------|----------------|
| | | 0.5 + y + x | 0.5 + N - y - x | | | |
| 0 | 0.00386 | 8.5 | 17.5 | 0.59701 | 0 | 0 |
| 1 | 0.01988 | 9.5 | 16.5 | 0.74873 | 0 | 0 |
| 2 | 0.05482 | 10.5 | 15.5 | 0.86166 | 0 | 0 |
| 3 | 0.10585 | 11.5 | 14.5 | 0.93311 | 1 | 0.10585 |
| 4 | 0.1578 | 12.5 | 13.5 | 0.97171 | 1 | 0.26365 |
| 5 | 0.18936 | 13.5 | 12.5 | 0.98958 | 1 | 0.45301 |
| 6 | 0.18524 | 14.5 | 11.5 | 0.99667 | 1 | 0.63825 |
| 7 | 0.14618 | 15.5 | 10.5 | 0.99908 | 1 | 0.78443 |
| 8 | 0.08944 | 16.5 | 9.5 | 0.99978 | 1 | 0.87387 |
| 9 | 0.03858 | 17.5 | 8.5 | 0.99996 | 1 | 0.91245 |
| 10 | 0.00900 | 18.5 | 7.5 | 0.99999 | 1 | 0.92145 |

THE SIMULATION ALGORITHM - MARKOV CHAIN MONTE CARLO

Markov Chain Monte Carlo (MCMC) is a vital simulation method to sample successively from posterior distribution, whose parameters can be updated by the prior distribution $p(p_E)$ and the likelihood function $L(y|p_E)$ given parameter p_E and the observed data y from Bayesian perspectives. Hence, the posterior density can be denoted as $\pi(p_E|y) \propto p(p_E) L(y|p_E)$ [6]. Each sample is related to the previous one.

Let p_E denote response rate and Y be the number of responses out of n treated subjects. We specify a non-informative Beta prior distribution for p_E , $p_E \sim \text{Beta}(0.5, 0.5)$ and $Y = y|p_E$ follows Binomial distribution, $y|p_E \sim \text{Bin}(n, p_E)$. We suppose closed-form solution of the posterior can't be obtained given the current y , namely X out of $(N - n)$ subjects enrolled in the future not following a Beta-Bin distribution and the posterior distribution of p_E given current data y and potential data x of responses will not be computed as Beta distribution. At this time, the simulation method can be used to calculate the predictive probability and we can get the $P(x | y)$ and $\text{Prob}(p_E > p_S | y, x)$ via the procedure of MCMC. Their SAS codes are shown in the part I and II, respectively. In the part II, m means $(N - n)$ subjects and there are $(m + 1)$ response scenarios for X at the second stage.

```

I. proc mcmc data = xxx nmc = xxxx seed = 1 outpost= xxx;
   parm p;
   prior p ~ beta (0.5, 0.5);
   model y ~ binomial (n, p);
   preddist outpred = xxx covariates = xxx; run;

II. proc mcmc data = xxx seed = 1 nmc = xxxx outpost = xxx;
   by scenario;
   parm p;
   prior p ~ beta (0.5, 0.5);
   model y ~ binomial(n,p);
   model success ~ binomial (m,p); run;

```

The predictive probability can be computed in Macro %**PPOS_MCMC** based on the simulation algorithm. Table 2 shows the results by Macro %**PPOS_MCMC** (Nmax = 25, n = 15, Y = 8, Ps = 0.3, theta_t = 0.9, a0 = 0.5, b0 = 0.5, print = ALL). The predictive probability is 0.92128, which is approximate to that by the exact algorithm.

Table 2 Results of Calculating the Predictive Probability by the MCMC Method

| X | P (x y) | Prob ($p_E > p_S y, x$) | | Indictor | | PP |
|----|-----------|-----------------------------|--|------------------|--|----------------|
| | | $p_S = 0.3$ | | $\theta_T = 0.9$ | | |
| 0 | 0.00396 | 0.59752 | | 0 | | 0 |
| 1 | 0.01996 | 0.74828 | | 0 | | 0 |
| 2 | 0.05480 | 0.86308 | | 0 | | 0 |
| 3 | 0.10656 | 0.93012 | | 1 | | 0.10656 |
| 4 | 0.15792 | 0.97048 | | 1 | | 0.26448 |
| 5 | 0.18504 | 0.98876 | | 1 | | 0.44952 |
| 6 | 0.18652 | 0.99612 | | 1 | | 0.63604 |
| 7 | 0.14596 | 0.99928 | | 1 | | 0.78200 |
| 8 | 0.09076 | 0.99980 | | 1 | | 0.87276 |
| 9 | 0.04024 | 0.99992 | | 1 | | 0.91300 |
| 10 | 0.00828 | 1 | | 1 | | 0.92128 |

Table 3 shows result comparisons between the exact and simulation algorithms. These results acquired with both ways are pretty similar. Hence, either one of both methods can be adopted to our clinical trials.

Table 3 Result Comparisons between the Exact and Simulation Algorithms

| X | P (x y) | | Prob ($p_E > p_S y, x$) | | Indictor | | PP | |
|---|-----------|---------|-----------------------------|---------|------------------|------|---------|---------|
| | | | $p_S = 0.3$ | | $\theta_T = 0.9$ | | | |
| | Exact | MCMC | Exact | MCMC | Exact | MCMC | Exact | MCMC |
| 0 | 0.00386 | 0.00396 | 0.59701 | 0.59752 | 0 | 0 | 0 | 0 |
| 1 | 0.01988 | 0.01996 | 0.74873 | 0.74828 | 0 | 0 | 0 | 0 |
| 2 | 0.05482 | 0.05480 | 0.86166 | 0.86308 | 0 | 0 | 0 | 0 |
| 3 | 0.10585 | 0.10656 | 0.93311 | 0.93012 | 1 | 1 | 0.10585 | 0.10656 |
| 4 | 0.1578 | 0.15792 | 0.97171 | 0.97048 | 1 | 1 | 0.26365 | 0.26448 |
| 5 | 0.18936 | 0.18504 | 0.98958 | 0.98876 | 1 | 1 | 0.45301 | 0.44952 |
| 6 | 0.18524 | 0.18652 | 0.99667 | 0.99612 | 1 | 1 | 0.63825 | 0.63604 |
| 7 | 0.14618 | 0.14596 | 0.99908 | 0.99928 | 1 | 1 | 0.78443 | 0.78200 |
| 8 | 0.08944 | 0.09076 | 0.99978 | 0.99980 | 1 | 1 | 0.87387 | 0.87276 |

| | | | | | | | | |
|----|---------|---------|---------|---------|---|---|----------------|----------------|
| 9 | 0.03858 | 0.04024 | 0.99996 | 0.99992 | 1 | 1 | 0.91245 | 0.91300 |
| 10 | 0.00900 | 0.00828 | 0.99999 | 1 | 1 | 1 | 0.92145 | 0.92128 |

Because of complex of predictive probabilities and operation difficulty for non-statisticians, it's necessary to convert predictive probabilities into convenient and digestible format. Predictive probabilities of any combinations of Y and n at interim analysis can be computed in advance. Therefore, futility and efficacy early stopping boundaries on number of subjects can be derived from them [7]. We assume the maximum sample size is 25 and apply early stopping rule before the minimum number of subjects is 5, the rest of parameters are used as mentioned previously. As shown in the Figure 1, red and green blocks represent futility and efficacy early stopping, respectively. Table 4 demonstrates early stopping boundaries for futility and efficacy, which is simple and friendly for investigators and clinical operation managers.

Figure 1 Predictive Probabilities for Early Stopping

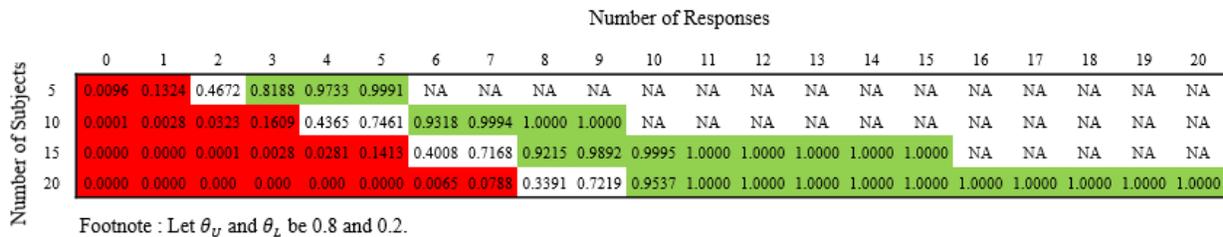


Table 4 Stopping Boundaries for Futility and Efficacy

| Subjects | Futility Stopping Boundaries (PP < 0.2) | Efficacy Stopping Boundaries (PP > 0.8) |
|----------|---|---|
| | Responses are considered futile | Responses are considered efficacious |
| 5 | ≤1 | ≥3 |
| 10 | ≤3 | ≥6 |
| 15 | ≤5 | ≥8 |
| 20 | ≤7 | ≥10 |

CONCLUSION

Continuous data monitoring is the importance of exploring drug efficacy at early phases. This paper reviews two different methods to calculate predictive probabilities for monitoring futility or efficacy and shows fairly similar results. Both methods are good fit on deriving predictive probabilities and which method to adopt only depends on the user's preferences. The appendix contains detailed codes of Macro **%PPOS** and **%PPOS_MCMC**.

REFERENCES

- [1] Simon R. Optimal two-stage designs for phase II clinical trials. *Cont Clin Trials*. 1989; 10:1–10.
- [2] Green SJ, Dahlberg S. Planned versus attained design in phase II clinical trials. *Statistics in Medicine*. 1992; 11:853–862.
- [3] Lee J J, Liu D D. A predictive probability design for phase II cancer clinical trials. *Clinical trials*. 2008; 5(2): 93-106.
- [4] Chen F. Bayesian modeling using the MCMC procedure[C]//*Proceedings of the SAS Global Forum 2008 Conference*, Cary NC: SAS Institute Inc. 2009.
- [5] Lesaffre E, Lawson A B. *Bayesian biostatistics[M]*. John Wiley & Sons, 2012.
- [6] Yin G. *Clinical trial design: Bayesian and frequentist adaptive methods[M]*. John Wiley & Sons, 2012.

[7] <https://trialdesign.org/one-page-shell.html#BEMPR>

APPENDIX

1. %macro PPOS:

```
%macro PPOS (Nmax,n,Y,Ps,theta_t,a0,b0,print = ALL);
%let m = &Nmax - &n;
%let alp = &a0 + &Y;
%let bet = &b0 + &n - &Y;
data ppos;
  PP = 0;
  do X = 0 to &m by 1;
    lgval = logbeta(&alp+X, &bet+&m-X)-logbeta(&alp,&bet)+lcomb(&m,X);
    PXY = exp(lgval);
    alp1 = &a0 + &Y + X;
    bet1 = &b0 + &Nmax - &Y - X;
    Prob = 1 - cdf("beta", &Ps,alp1 , bet1);
    if Prob > &theta_t then ID = 1;
    else ID = 0;
    PP = PP + PXY * ID;
  output;
end;
keep X PXY alp1 bet1 Prob ID PP;
proc print;
run;
%mend PPOS;
```

2. %macro PPOS_MCMC:

```
%macro PPOS_MCMC (Nmax, n, Y, Ps,theta_t,a0,b0,print = ALL);
%let m = &Nmax - &n;
data ia; y = &Y; n = &n; run;
data predx; n = &m; run;

/*simulation of X=x*/
proc mcmc data = ia nmc = 25000 seed = 1 outpost=outpost;
  parm p;
  prior p ~ beta (&a0, &b0);
  model y ~ binomial (n, p);
run;
```

```

preddist outpred=outx covariates=predx;
run;

/*summary P(x|y)*/
proc freq data= outx; tables y_1 /out= summ_y; run;
data summy1(drop=COUNT PERCENT);
  set summ_y;
  PXY = PERCENT*0.01;
run;

data summy2;
  do i = 0 to &m;
    y_1=i;output;
  end;
run;

proc sql noprint;
  create table prxy(drop=i) as select
  summy2.*, case when summy1.y_1^=. then summy1.PXY else 0 end as
PXY
  from summy2
  left join summy1 on summy2.y_1=summy1.y_1;
quit;
proc sort data=prxy; by y_1; run;

/*simulation of Prob(Pe>Ps|y,x)*/
data dd (drop=i rename=(var1=success var2=scenario));
do i = 0 to &m;
  y=&Y;
  n=&n;
  m=&m;
  var1=i;
  var2=i+1;
  output;
end;
run;

```

```

proc mcmc data=dd seed=1 nmc=25000 outpost=outprob;
  by scenario;
  parm p;
  prior p ~ beta(&a0,&b0);
  model y ~ binomial(n,p);
  model success ~ binomial(m,p);
run;

/*summary Prob(Pe>Ps|y,x)*/
data outprob1; set outprob; if p>&Ps then output; run;
proc freq data=outprob1;
tables scenario /out=summprob (drop=PERCENT); run;

data summprob1(drop=COUNT scenario);
  set summprob;
  Prob=COUNT/25000;
  y_1=scenario-1;
proc sort;
by y_1;
run;

data final;
merge prxy(in=a)
      summprob1(in=b)
      ;
  by y_1;
  if a and b;
  run;

data ppos(rename=y_1=x);
  set final;
  retain PP 0;
  if Prob> &theta_t then ID=1;
  else ID=0;
  PP= PP+PXY*ID;
proc print;run;
%mend PPOS_MCMC;

```

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