SHP2 + IO Combo Simulation (v6)

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# 1 Methods

## 1.1 Calculating predictive probabilities via simulation

### 1.1.1 Predictive Probability (PP) of Success

* **Definition**: The probability of achieving a successful (significant) result at a future analysis, given the current interim data;
* Obtained by integrating the data likelihood over the posterior distribution (i.e. we integrate over future possible responses) and predicting the future outcome of the trial;
* Efficacy rules can be based either on Bayesian posterior distributions (fully Bayesian) or frequentist p-values (mixed Bayesian-frequentist)

### 1.1.2 Description of algorithm

1. A phase II study is designed to test:
2. The Type I & II error are defined as
3. Set a maximum accrual of patients to
4. **Assume** the prior distribution of response rate follows a beta distribution
5. **Assume** the responders in the current , , follows a binomial distribution ;

Based on this the posterior distribution of the follows a beta distribution ( is the observed responders)

Thus, the number of responders in the potential future patients, follows a beta-binomial distribution

1. The posterior of given and is
2. Define the probability that the response rate is larger than given in the the current stage data ( patients) and in the future patients;
3. Comparing to a threshold yields an indicator for the efficacious at the end of the trial given the current data and potential future outcome
4. Compute the Predictive Probability (PP)
5. Based on the PP given in the below tables, we could decide whether the trial should be stopped if PP is **sufficiently low**.

In the work of Lee, J. J., Liu, D. D. (2008), 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 sufficient activity.

Typically, we choose as a small positive number and as a large positive constant, both between 0 and 1 (inclusive).

* If , then stop the trial and reject the alternative hypothesis (futility);
* If , then stop the trial and reject the null hypothesis (efficacious);
* Otherwise, continue to the next stage until reaching the total sample size.

### 1.1.3 Type I/II error and power calculation using simulation methods

The phase II study is designed to test:

The Type I & II error are defined as

The general view of testing the operating characteristics of a design using PP methods via simulations is (suppose a 2-stage design):

1. Set parameters for design
2. Under (), the Type I error is Accept new treatment , which is

* success in 1st interim analysis and final analysis: in 1st interim analysis go to final analysis success in final analysis

1. Under (), the Type II error is Reject new treatment , which is

* fail in 1st interim analysis **or** success in 1st interim analysis but fail in final analysis:
  + in 1st interim analysis, stop; **or**
  + in 1st interim analysis go to final analysis fail in final analysis (total responders in final analysis (Lee, J. J., Liu, D. D. (2008)))

The function for assessing the operating characteristics of a 2-stage design via simulation is provided as:

OC <- function(numrep,a0,b0,p0,p1,r,n1,ntotal,thetat,thetal){  
 alpha <- rep(0, numrep)  
 beta <- rep(0, numrep)  
 et <- rep(0, numrep)  
 for (rep in (1:numrep)) {  
 v1 <- rbinom(n = n1, size = 1, prob = p0)  
 v2 <- rbinom(n = ntotal - n1,size = 1,prob = p0)  
 betav1 <- rbinom(n = n1, size = 1, prob = p1)  
 betav2 <- rbinom(n = ntotal - n1,size = 1,prob = p1)  
 sumv1 <- sum(v1)  
 sumv2 <- sum(v2)  
 betasumv1 <- sum(betav1)  
 betasumv2 <- sum(betav2)  
 pp <-  
 PredP(  
 x = sumv1,  
 n = n1,  
 nmax = ntotal,  
 a = a0,  
 b = b0,  
 p0 = p0,  
 theta\_t = thetat  
 )  
 ppbeta <-  
 PredP(  
 x = betasumv1,  
 n = n1,  
 nmax = ntotal,  
 a = a0,  
 b = b0,  
 p0 = p0,  
 theta\_t = thetat  
 )  
 if (pp >= thetal) {  
 totalr <- sumv2 + sumv1  
 rlogic <- totalr > r  
 alpha[rep] <- TRUE \* rlogic  
 } else {  
 et[rep] <- TRUE  
 }  
 if (ppbeta >= thetal) {  
 betatotalr <- betasumv2 + betasumv1  
 betarlogic <- betatotalr <= r  
 beta[rep] <- TRUE \* betarlogic  
 } else {  
 beta[rep] <- TRUE  
 }  
 }  
 # cat("early stopping is:", mean(et), "\n")  
 # cat("type i error:", mean(alpha), "\n")  
 # cat("type ii error:", mean(beta), "\n")  
 # cat("power:", 1 - mean(beta))  
 final <- c(mean(alpha),mean(beta))  
 return(final)  
}

The function for assessing the Type I error of a 3-stage design via simulation is provided as:

ThreeStageOC <- function(numrep,a0,b0,p0,p1,r,n1,n2,n3,ntotal,thetat,thetal){  
 alpha <- rep(0, numrep)  
 for (rep in (1:numrep)) {  
 v1 <- rbinom(n = n1, size = 1, prob = p0)  
 v2 <- rbinom(n = n2, size = 1, prob = p0)  
 v3 <- rbinom(n = ntotal - n1 - n2,size = 1,prob = p0)  
 sumv1 <- sum(v1)  
 sumv2 <- sum(v2)  
 sumv3 <- sum(v3)  
 pp1 <-  
 PredP(  
 x = sumv1,  
 n = n1,  
 nmax = ntotal,  
 a = a0,  
 b = b0,  
 p0 = p0,  
 theta\_t = thetat  
 )  
 pp2 <-  
 PredP(  
 x = sumv1+sumv2,  
 n = n1+n2,  
 nmax = ntotal,  
 a = a0,  
 b = b0,  
 p0 = p0,  
 theta\_t = thetat  
 )  
 if (pp1 >= thetal) {  
 if (pp2 >= thetal){  
 totalr <- sumv3 + sumv2 + sumv1  
 rlogic <- totalr > r  
 alpha[rep] <- TRUE \* rlogic  
 }  
 }   
 }  
 cat("type i error:", mean(alpha), "\n")  
}

# 2 Scenario 1

## 2.1 Objective

To determine the expected sample size and target responders

## 2.2 Parameters

1. Set a target response rate for simulate purpose (**need medical input**)

psim <- 0.3

1. 1st stage total subjects (**we assume this is a point we will look at**)

n1 <- 10

1. Total sample size (**we assume this is pre-specified prior to the beginning of trial**)

ss <- 36  
ss

## [1] 36

1. Success criteria

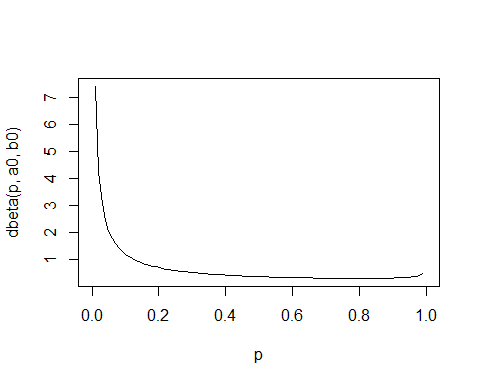
* Pre-specified response rate for standard treatment: (**need medical input**)
* Pre-specified response rate for new treatment: (**need medical input if Type II error rate and Power are needed to be evaluated**)
* Threshold for considering *the treatment is efficacious at the end of the trial* given the current data and the potential outcome of future responders ( in the above): (**need medical input**)
* The boundary for stopping the trial and reject the alternative hypothesis for futility (cutoff of the predictive probability to indicate unfavorable likelihood for success): (**need medical input**)

p\_0 <- 0.2  
p\_1 <- 0.4  
thetat <- 0.855  
thetal <- 0.001

1. Prior hyper-parameters

The response rate follows a beta distribution (**medical should input the response rate estimate**) where

a0 <- 0.2  
b0 <- 0.8  
# define range for plot  
p = seq(0,1, length=100)  
# create plot of Beta distribution with shape parameters a0 and b0  
plot(p, dbeta(p, a0, b0), type='l')



## 2.3 Simulation Code & Results

# call library ph2bye  
library(ph2bye)  
library(dplyr)  
library(ggplot2)  
library(huxtable)

#Lee and Liu's criterion function for determining the trial decision cutoffs based on the predictive probability  
ppfunc <- function(mink,n1,nmax,a0,b0,p0,thetat){  
 # construct empty matrix  
 empmat <- data.frame(matrix(0,min(mink+1,n1+1),3))  
 colnames(empmat) <- c("totalsample","responders","pp")  
 # responders in stage 1  
 resp\_s1 <- seq(0,min(mink,n1),1)  
 for (i in 1:length(resp\_s1)){  
 empmat[i,1] <- nmax  
 empmat[i,2] <- resp\_s1[i]  
 pp <- PredP(x=resp\_s1[i], n=n1, nmax=nmax, a=a0, b=b0, p0=p0, theta\_t=thetat)  
 empmat[i,3] <- pp  
 }  
 return(empmat)  
}

### 2.3.1 General considerations for PP

*Note that in the following tables, column “responders” means that the number of observed responders in 1st stage during the trial.*

### 2.3.2 Total sample size of 36 patients enrolled in the first stage.

#### 2.3.2.1 0. simulate analysis dataset

set.seed(2022)  
  
# create the analysis data set for stage I   
date1 <- as.character(rep(as.Date("2022-01-29"),n1))  
respond1 <- rbinom(n1,1,psim)  
# actual number of responders in stage 1  
actr1 <- sum(respond1)  
subjid <- as.character(seq(1001,1001+n1-1,by=1))  
stage1df <- as\_hux(data.frame(subjid=subjid,datetime=date1,response=respond1))  
stage1df %>%  
 set\_all\_padding(4) %>%  
 set\_outer\_padding(0) %>%  
 set\_font\_size(9) %>%  
 set\_bold(row = 1, col = everywhere) %>%  
 set\_bottom\_border(row = 1, col = everywhere) %>%  
 set\_width(0.4) %>%  
 set\_caption("simulated dataset for stage 1")

**Table 1**: simulated dataset for stage 1

|  |  |  |
| --- | --- | --- |
| **subjid** | **datetime** | **response** |
| 1001 | 2022-01-29 | 1 |
| 1002 | 2022-01-29 | 0 |
| 1003 | 2022-01-29 | 0 |
| 1004 | 2022-01-29 | 0 |
| 1005 | 2022-01-29 | 0 |
| 1006 | 2022-01-29 | 0 |
| 1007 | 2022-01-29 | 0 |
| 1008 | 2022-01-29 | 0 |
| 1009 | 2022-01-29 | 0 |
| 1010 | 2022-01-29 | 1 |

#### 2.3.2.2 Find the target number of responders during the trial

##### 2.3.2.2.1 calculate minimum k (Chen DT, et al (2019))

With the assumptions above, we need to calculate the minimum of responders needed at the end of trial to claim efficacy by comparing the posterior probability of response rate and threshold , given :

Based on the current information, we can calculate the expected minimum responders needed at the end of trial to claim efficacy:

for (k in 1:(ss-1)){  
 pminik <- beta(a0,b0)\*(pbeta(1,a0+k,b0+ss-k)-pbeta(p\_0,a0+k,b0+ss-k))-thetat  
 if (pminik>0){  
 cat("The expected minimum responders needed at the end of trial to claim efficacy is:",k)  
 minik<- k  
 break  
 }  
}

## The expected minimum responders needed at the end of trial to claim efficacy is: 6

##### 2.3.2.2.2 \*calculate target responders (Lee, J. J., Liu, D. D. (2008))

Given the parameters - Total sample size: ss - Prior hyper-parameters: a0, b0 - Response rate for the standard drug under null hypothesis: p0 - Cutoff probability for efficacy including future patients: thetat - Cutoff probability for futility based on PP: thetal

We can search the target responders (or rejection region) based on a given total sample size.

DesignA <- PredP.design(type = "futility", nmax=ss, a=a0, b=b0, p0=p\_0, theta\_t=thetat ,theta=thetal)  
  
DesignAhux <- as\_hux(DesignA)  
DesignAhux %>%  
 set\_all\_padding(4) %>%  
 set\_outer\_padding(0) %>%  
 set\_font\_size(9) %>%  
 set\_bold(row = 1, col = everywhere) %>%  
 set\_bottom\_border(row = 1, col = everywhere) %>%  
 set\_width(0.4) %>%  
 set\_caption("boundary")

**Table 2**: boundary

|  |  |
| --- | --- |
| **n** | **bound** |
| 1 |  |
| 2 |  |
| 3 |  |
| 4 |  |
| 5 |  |
| 6 |  |
| 7 |  |
| 8 |  |
| 9 |  |
| 10 | 0 |
| 11 | 0 |
| 12 | 0 |
| 13 | 0 |
| 14 | 0 |
| 15 | 0 |
| 16 | 0 |
| 17 | 1 |
| 18 | 1 |
| 19 | 1 |
| 20 | 1 |
| 21 | 2 |
| 22 | 2 |
| 23 | 2 |
| 24 | 3 |
| 25 | 3 |
| 26 | 3 |
| 27 | 4 |
| 28 | 4 |
| 29 | 5 |
| 30 | 5 |
| 31 | 6 |
| 32 | 6 |
| 33 | 7 |
| 34 | 8 |
| 35 | 9 |
| 36 | 10 |

From the above report, 10/36 (responders/Total patients) is the rejection region. Since when we observe responders in total 36 patients, the PP will be 0:

PredP(x=10, n=36, nmax=36, a=a0, b=b0, p0=p\_0, theta\_t=thetat)

## [1] 0

Therefore, the number of target responders with this sample size should be .

PredP(x=11, n=36, nmax=36, a=a0, b=b0, p0=p\_0, theta\_t=thetat)

## [1] 1

**Note**

In the algorithm (Lee, J. J., Liu, D. D. (2008)), we should search thetat and thetal to satisfy the constraints of Type I and Type II error rates.

##### 2.3.2.2.3 consider a 2-stage design

Consider a design with 2 planned interim analyses with 10 20 patients in the 1st, and final stage. Given we need to search thetal and thetat.

As an example, we will stop the searching when the thetal and thetat satisfy the constraints Type I error rates and Type II error rate (just for illustration).

gridThetat <- seq(0.860,0.900,0.001)  
gridThetal <- seq(0.001,0.010,0.001)  
numrep <- 5000  
stop <- FALSE  
  
for (i in 1:length(gridThetat)) {  
 for (j in 1:length(gridThetal)) {  
 oseva <-  
 OC(  
 numrep = numrep,  
 a0 = a0,  
 b0 = b0,  
 p0 = p\_0,  
 p1 = p\_1,  
 r = 10,  
 n1 = n1,  
 ntotal = ss,  
 thetat = gridThetat[i],  
 thetal = gridThetal[j]  
 )  
 # ??? is it correct?  
 pp <- PredP(x=11, n=36, nmax=36, a=a0, b=b0, p0=p\_0, theta\_t=gridThetat[i])  
   
 # constraints: alpha <= 0.10 and beta <= 0.10  
 if ((oseva[1] <= 0.10) && (oseva[2] <= 0.10) && (pp>=1)) {  
 stop <- TRUE  
 thetat1 <- gridThetat[i]  
 thetal1 <- gridThetal[j]  
 break  
 } else {  
 next  
 }  
 }  
 if (stop == TRUE) {  
 break  
 }  
}  
  
cat("theta\_t should be: ", thetat1, "\n")

## theta\_t should be: 0.86

cat("theta\_l should be: ", thetal1)

## theta\_l should be: 0.001

**Then we can use these two parameters for further analysis.**

# reset parameters for the following formal analysis  
thetal <- 0.001  
thetat <- 0.86

#### 2.3.2.3 simulate the number of patients with response in the 1st interim analysis with 10 patients

We list the predictivity probability for all scenarios of number of responders in the first 10 patients (1st interim analysis) and number of responders needed in the remaining patients to have at least a total of responders (Lee, J. J., Liu, D. D. (2008)).

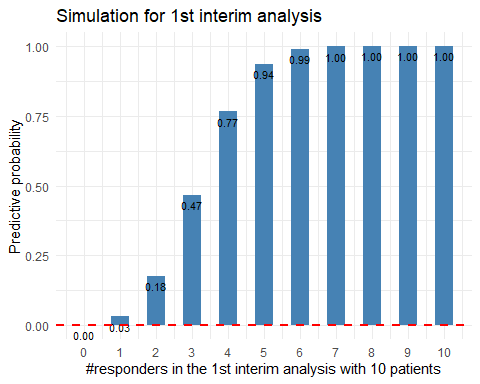
result <-  
 ppfunc(  
 mink = 11, # target number of responders  
 n1 = n1,  
 nmax = 36,  
 a0 = a0,  
 b0 = b0,  
 p0 = p\_0,  
 thetat = thetat  
 )  
resulthux <- as\_hux(result)  
resulthux %>%  
 set\_all\_padding(4) %>%  
 set\_outer\_padding(0) %>%  
 set\_font\_size(9) %>%  
 set\_bold(row = 1, col = everywhere) %>%  
 set\_bottom\_border(row = 1, col = everywhere) %>%  
 set\_width(0.4) %>%  
 set\_caption("predictive probability based on the results of stage 1") %>%  
 set\_text\_color(row = 4, value = "red")

**Table 3**: predictive probability based on the results of stage 1

|  |  |  |
| --- | --- | --- |
| **totalsample** | **responders** | **pp** |
| 36 | 0 | 0.000756 |
| 36 | 1 | 0.0311 |
| 36 | 2 | 0.177 |
| 36 | 3 | 0.468 |
| 36 | 4 | 0.766 |
| 36 | 5 | 0.936 |
| 36 | 6 | 0.99 |
| 36 | 7 | 0.999 |
| 36 | 8 | 1 |
| 36 | 9 | 1 |
| 36 | 10 | 1 |

The plot is

x\_axis\_labels <- 0:10  
p <-  
 ggplot(data = result, aes(  
 x = responders,  
 y = pp  
 )) +  
 geom\_bar(stat = "identity", fill = "steelblue", width = 0.5) +  
 labs(title = "Simulation for 1st interim analysis", x = "#responders in the 1st interim analysis with 10 patients", y = "Predictive probability") +  
 geom\_text(aes(label = sprintf("%0.2f", pp)),  
 vjust = 1.6,  
 color = "black",  
 size = 3) +  
 scale\_x\_continuous(labels = x\_axis\_labels, breaks = x\_axis\_labels)+  
 geom\_hline(yintercept=thetal, linetype="dashed", color = "red", size=1)+  
 theme\_minimal()  
p



Since we observe 2 responders in the 1st interim analysis, we can go to next stage.

#### 2.3.2.4 simulate the number of patients with response in the final analysis with 26 patients

# create the analysis data set for stage II   
date2 <- as.character(rep(as.Date("2022-03-29"),ss-n1))  
respond2 <- rbinom(ss-n1,1,psim)  
# actual number of responders in stage 1  
actr2 <- sum(respond2)  
cat("Number of responders in stage 2: ",actr2)

## Number of responders in stage 2: 12

subjid2 <- as.character(seq(1001+n1,1001+ss-1,by=1))  
stage2df <- as\_hux(data.frame(subjid=subjid2,datetime=date2,response=respond2))  
stage2df %>%  
 set\_all\_padding(4) %>%  
 set\_outer\_padding(0) %>%  
 set\_font\_size(9) %>%  
 set\_bold(row = 1, col = everywhere) %>%  
 set\_bottom\_border(row = 1, col = everywhere) %>%  
 set\_width(0.4) %>%  
 set\_caption("simulated dataset for stage 2")

**Table 4**: simulated dataset for stage 2

|  |  |  |
| --- | --- | --- |
| **subjid** | **datetime** | **response** |
| 1011 | 2022-03-29 | 1 |
| 1012 | 2022-03-29 | 0 |
| 1013 | 2022-03-29 | 0 |
| 1014 | 2022-03-29 | 0 |
| 1015 | 2022-03-29 | 0 |
| 1016 | 2022-03-29 | 0 |
| 1017 | 2022-03-29 | 1 |
| 1018 | 2022-03-29 | 0 |
| 1019 | 2022-03-29 | 0 |
| 1020 | 2022-03-29 | 1 |
| 1021 | 2022-03-29 | 1 |
| 1022 | 2022-03-29 | 0 |
| 1023 | 2022-03-29 | 0 |
| 1024 | 2022-03-29 | 0 |
| 1025 | 2022-03-29 | 0 |
| 1026 | 2022-03-29 | 1 |
| 1027 | 2022-03-29 | 1 |
| 1028 | 2022-03-29 | 0 |
| 1029 | 2022-03-29 | 1 |
| 1030 | 2022-03-29 | 1 |
| 1031 | 2022-03-29 | 1 |
| 1032 | 2022-03-29 | 1 |
| 1033 | 2022-03-29 | 1 |
| 1034 | 2022-03-29 | 0 |
| 1035 | 2022-03-29 | 1 |
| 1036 | 2022-03-29 | 0 |

Based on the 12 responders, we have total 14 responders in the trial which is **larger than 10**.

**We will consider the new treatment since it warrants further development.**

# 3 Discussion

## 3.1 Given total sample size, varing responders to search and

Suppose total sample size is still 36, we vary the number of responders from 6 to 15 to find the combination of , and satisfying the constraints of Type I and Type II error rates.

The results are given in the appendix B.

# set the constaints for Type I/II error rates  
typei <- 0.05  
typeii <- 0.20  
  
# the range of parameters  
gridr <- seq(6,15,1)  
gridThetal <- seq(0.001,0.03,0.001)  
gridThetat <- seq(0.70,0.95,0.001)  
numrep <- 4000  
  
# function to search the combination of parameters  
searchPara <-  
 function(gridr,  
 gridThetat,  
 gridThetal,  
 nmax,  
 n1,  
 a,  
 b,  
 p0,  
 p1,  
 repnum,  
 alpha,  
 beta) {  
   
 mat <- matrix(NA, 1000, 6)  
 rowindex <- 1  
   
 for (r in gridr) {  
 for (i in 1:length(gridThetat)) {  
 for (j in 1:length(gridThetal)) {  
 rejreg <-  
 PredP.design(  
 type = "futility",  
 nmax = nmax,  
 a = a,  
 b = b,  
 p0 = p0,  
 theta = gridThetal[j]  
 )  
 rejbound <- tail(rejreg$bound, n = 1)  
   
 if (!(rejbound == r)) {  
 break  
 } else {  
 oseva <-  
 OC(  
 numrep = numrep,  
 a0 = a,  
 b0 = b,  
 p0 = p0,  
 p1 = p1,  
 r = r + 1,  
 n1 = n1,  
 ntotal = nmax,  
 thetat = gridThetat[i],  
 thetal = gridThetal[j]  
 )  
   
 # constraints: alpha <= 0.10 and beta <= 0.10  
 if ((oseva[1] <= alpha) && (oseva[2] <= beta) && (rowindex <= 1000)) {  
 stop <- TRUE  
 thetat1 <- gridThetat[i]  
 thetal1 <- gridThetal[j]  
 mat[rowindex, 1] <- nmax  
 mat[rowindex, 2] <- r  
 mat[rowindex, 3] <- thetat1  
 mat[rowindex, 4] <- thetal1  
 mat[rowindex, 5] <- oseva[1]  
 mat[rowindex, 6] <- oseva[2]  
 rowindex <- rowindex + 1  
 break  
 }  
 }  
 }  
   
 if (stop == TRUE) {next}  
 }  
 }  
 df <- data.frame(mat)  
 colnames(df) <- c("N","r","theta\_t","theta\_l","Type\_I","Type\_II")  
 df <- df[complete.cases(df), ]  
 return(df)  
 }

## 3.2 The choice of parameters for beta prior

Information about response data of the experimental treatment helps determine the beta prior distribution, , for the response rate where

* represents the degree of response (e.g., number of responders)
* indicates magnitude of non-response (e.g., number of non-responders).

The mean response rate is with

* for tendency of more drug-sensitive
* for more drug-resistant
* for undetermined.

In addition, when becomes large, the belief of prior information gets strong and likely dominates the result.

While many experimental treatments are usually the first study, some of them are a combination of standard treatment with new drug or modification of standard treatment. Thus, **utilization of historical data** could help better shape prior distribution within the Bayesian framework.

Often prior information provided by a physician is not the values of and , but a **response rate estimate**. Conversion to the two parameters ( and ) can be done by a formula with a hypothesized standard deviation (SD) of response rate ():

## 3.3 Minimally informative prior distribution

Minimally informative (less direct but synonymous terms are *diffuse*, *weak*, and *vague*) priors fall into two broad classes:

1. so-called non-informative priors, which attempt to be completely objective, in that the posterior distribution is determined as completely as possible by the observed data, the most well known example in this class being the Jeffreys prior (for beta distribution it’s ), and
2. priors that are diffuse over the region where the likelihood function is non-negligible, but that incorporate some information about the parameters being estimated, such as a mean value.

In contrast, the use of informative prior distributions explicitly acknowledges that the analysis is based on more than the immediate data in hand whose relevance to the parameters of interest is modelled through the likelihood, and also includes a considered judgement concerning plausible values of the parameters based on external information.

**In fact the division between these two options is not so clear-cut** — in particular, we would claim that any “objective” Bayesian analysis is a lot more “subjective” than it may wish to appear.

* First, any statistical model (Bayesian or otherwise) requires qualitative judgement in selecting its structure and distributional assumptions, regardless of whether informative prior distributions are adopted.
* Second, except in rather simple situations there may not be an agreed “objective” prior, and apparently innocuous assumptions can strongly inﬂuence conclusions in some circumstances.

## 3.4 The impact of choosing different a and b for beta(a,b)

1. If we have **little** or **no prior information**, or we want to **put very little stock in the information we have**, we can choose values for and that reduce the distribution to a uniform distribution.

For example, if we let and , we get which is proportional to a uniform distribution on the allowable interval for response rate ().

That is, the prior distribution is **ﬂat, not producing greater a priori weight for any value of over another**. Thus, the prior distribution will have little effect on the posterior distribution. For this reason, this type of prior is called “non-informative.”

1. At the opposite extreme, if we have **considerable prior information** and we want it to weigh heavily relative to the current data, we can use **large values** of and .

A little algebraic manipulation of the formula for the variance reveals that, **as and increase, the variance decreases**, which makes sense, because adding additional prior information ought to reduce our uncertainty about the parameter.

Thus, adding more prior successes and failures (increasing both parameters) reduces prior uncertainty about the parameter of interest ().

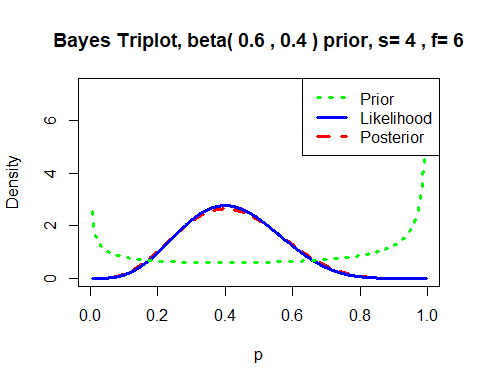
1. Finally, if we have considerable prior information but we do not wish for it to weigh heavily in the posterior distribution, we can choose moderate values of the parameters that yield a mean that is consistent with the previous research but that also produce a variance around that mean that is broad.

## 3.5 Example for the relationship among Prior/Likelihood/Posterior

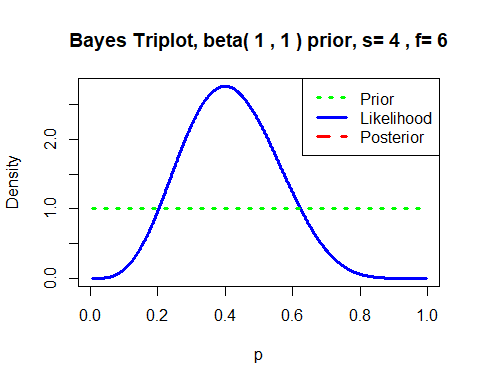
### 3.5.1 Minimally informative prior /

We can see that the prior distribution / has little effect on the posterior distribution.

library(LearnBayes)  
  
prior=c(0.6,0.4) # proportion has a beta(0.6, 0.4) prior  
data=c(4,6) # observe 4 successes and 6 failures based on our simulated dataset  
triplot(prior,data)



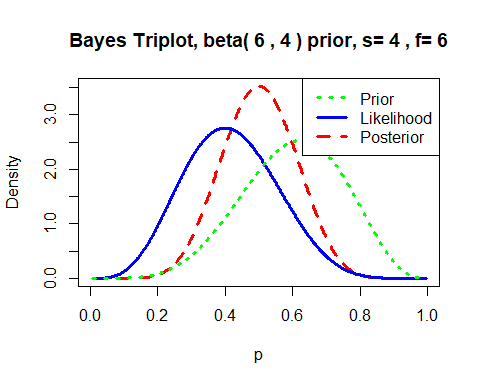
prior=c(1,1) # proportion has a beta(1, 1) prior  
data=c(4,6) # observe 4 successes and 6 failures based on our simulated dataset  
triplot(prior,data)



### 3.5.2 Informative prior

We can see that the prior distribution has considerable prior information and weigh heavily in the posterior distribution.

prior=c(6,4) # proportion has a beta(6, 4) prior  
data=c(4,6) # observe 4 successes and 6 failures based on our simulated dataset  
triplot(prior,data)



# 4 Appendix A

## 4.1 Type I error and power calculation using analytical methods

### 4.1.1 Method 1

*Dong, G., et al (2012)*

For the ﬁrst stage, patients are enrolled in the study. If the number of responses at 1st stage is greater than or equal to the upper boundary (), then reject the null hypothesis () and stop the trial for efﬁcacy. The **probability of rejecting the null hypothesis** is

where denotes cumulative binomial distribution function.

If (the lower boundary), then accept the null hypothesis and stop the trial because of futility. The probability of accepting the null hypothesis is

Otherwise, if is between and **()**, then continue the trial and enroll patients into 2nd stage.

Suppose there are responses observed in the patients in 2nd stage. If the cumulative number of the responses is greater than or equal to (), then reject the null hypothesis and claim that further investigation of the study therapy is warranted. The probability of rejecting the null hypothesis at the 2nd stage is

where is the probability density function of binomial distribution. Otherwise, the test treatment is not promising and no further investigation is warranted.

For the frequentist setting, it is important to control Type I error rate and maintain study power:

**Type I error rate**

**Power**

### 4.1.2 Method 2

*Chen DT, et al (2019)*

First of all, is the minimum of responders to claim efficacy with a total of patients, and is the number of responders for the stopping boundary at th stage to indicate unfavorable likelihood for success. Here we have

where is the additional number of responders needed in stage .

For , which is the stopping boundary at th stage can be easily calculated by the beta-binomial distribution

To find the minimum with searching to meet

where is the cut-off of the predictive probability, is the remaining patients given responders in the current stage of interim analysis.

**Define PET:** It is a probability to stop the trial before going to the final stage. For a two-stage design, it is the **probability of trial termination at the 1st stage**:

**Type I error:** It is a probability of accepting treatment efficacy when the true response rate is . The probability is the sum of and the probability of failure to reach the efficacy at the final stage. That is, for a stage design,

For a 2-stage design, Type I error is

**Power:** It is a probability of claiming efficacy when the true response rate is . That is,

# 5 Appendix B

# run  
sim1 <- searchPara(  
 gridr = gridr,  
 gridThetat = gridThetat,  
 gridThetal = gridThetal,  
 nmax = ss,  
 n1 = n1,  
 a = a0,  
 b = b0,  
 p0 = p\_0,  
 p1 = p\_1,  
 repnum = numrep,  
 alpha = typei,  
 beta = typeii  
)  
  
sim1hux <- as\_hux(sim1)  
sim1hux %>%  
 set\_all\_padding(4) %>%  
 set\_outer\_padding(0) %>%  
 set\_font\_size(8) %>%  
 set\_bold(row = 1, col = everywhere) %>%  
 set\_bottom\_border(row = 1, col = everywhere) %>%  
 set\_caption("The result of searching the combination of r, theta\_t and theta\_l with fixed total sample size")

**Table 5**: The result of searching the combination of r, theta\_t and theta\_l with fixed total sample size

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **N** | **r** | **theta\_t** | **theta\_l** | **Type\_I** | **Type\_II** |
| 36 | 10 | 0.7 | 0.001 | 0.0382 | 0.166 |
| 36 | 10 | 0.701 | 0.001 | 0.0475 | 0.165 |
| 36 | 10 | 0.702 | 0.001 | 0.0415 | 0.169 |
| 36 | 10 | 0.703 | 0.001 | 0.0475 | 0.164 |
| 36 | 10 | 0.704 | 0.001 | 0.0418 | 0.158 |
| 36 | 10 | 0.705 | 0.001 | 0.042 | 0.168 |
| 36 | 10 | 0.706 | 0.001 | 0.0345 | 0.161 |
| 36 | 10 | 0.707 | 0.001 | 0.0408 | 0.159 |
| 36 | 10 | 0.708 | 0.001 | 0.0413 | 0.171 |
| 36 | 10 | 0.709 | 0.001 | 0.0365 | 0.163 |
| 36 | 10 | 0.71 | 0.001 | 0.0408 | 0.155 |
| 36 | 10 | 0.711 | 0.001 | 0.0385 | 0.167 |
| 36 | 10 | 0.712 | 0.001 | 0.0455 | 0.164 |
| 36 | 10 | 0.713 | 0.001 | 0.043 | 0.163 |
| 36 | 10 | 0.714 | 0.001 | 0.0372 | 0.163 |
| 36 | 10 | 0.715 | 0.001 | 0.0423 | 0.156 |
| 36 | 10 | 0.716 | 0.001 | 0.0398 | 0.157 |
| 36 | 10 | 0.717 | 0.001 | 0.04 | 0.167 |
| 36 | 10 | 0.718 | 0.001 | 0.0413 | 0.158 |
| 36 | 10 | 0.719 | 0.001 | 0.0403 | 0.167 |
| 36 | 10 | 0.72 | 0.001 | 0.0432 | 0.166 |
| 36 | 10 | 0.721 | 0.001 | 0.0428 | 0.163 |
| 36 | 10 | 0.722 | 0.001 | 0.04 | 0.173 |
| 36 | 10 | 0.723 | 0.001 | 0.0415 | 0.159 |
| 36 | 10 | 0.724 | 0.001 | 0.0408 | 0.172 |
| 36 | 10 | 0.725 | 0.001 | 0.0408 | 0.154 |
| 36 | 10 | 0.726 | 0.001 | 0.043 | 0.168 |
| 36 | 10 | 0.727 | 0.001 | 0.043 | 0.161 |
| 36 | 10 | 0.728 | 0.001 | 0.043 | 0.168 |
| 36 | 10 | 0.729 | 0.001 | 0.048 | 0.16 |
| 36 | 10 | 0.73 | 0.001 | 0.037 | 0.16 |
| 36 | 10 | 0.731 | 0.001 | 0.0382 | 0.153 |
| 36 | 10 | 0.732 | 0.001 | 0.0445 | 0.159 |
| 36 | 10 | 0.733 | 0.001 | 0.0445 | 0.162 |
| 36 | 10 | 0.734 | 0.001 | 0.0472 | 0.152 |
| 36 | 10 | 0.735 | 0.001 | 0.0478 | 0.16 |
| 36 | 10 | 0.736 | 0.001 | 0.0398 | 0.167 |
| 36 | 10 | 0.737 | 0.001 | 0.045 | 0.162 |
| 36 | 10 | 0.738 | 0.001 | 0.0415 | 0.171 |
| 36 | 10 | 0.739 | 0.001 | 0.0398 | 0.173 |
| 36 | 10 | 0.74 | 0.001 | 0.0452 | 0.158 |
| 36 | 10 | 0.741 | 0.001 | 0.0425 | 0.17 |
| 36 | 10 | 0.742 | 0.001 | 0.0425 | 0.168 |
| 36 | 10 | 0.743 | 0.001 | 0.0445 | 0.164 |
| 36 | 10 | 0.744 | 0.001 | 0.0365 | 0.168 |
| 36 | 10 | 0.745 | 0.001 | 0.041 | 0.161 |
| 36 | 10 | 0.746 | 0.001 | 0.0423 | 0.17 |
| 36 | 10 | 0.747 | 0.001 | 0.046 | 0.152 |
| 36 | 10 | 0.748 | 0.001 | 0.0355 | 0.157 |
| 36 | 10 | 0.749 | 0.001 | 0.0457 | 0.168 |
| 36 | 10 | 0.75 | 0.001 | 0.0493 | 0.162 |
| 36 | 10 | 0.751 | 0.001 | 0.0437 | 0.161 |
| 36 | 10 | 0.752 | 0.001 | 0.0415 | 0.16 |
| 36 | 10 | 0.753 | 0.001 | 0.0395 | 0.169 |
| 36 | 10 | 0.754 | 0.001 | 0.0483 | 0.159 |
| 36 | 10 | 0.755 | 0.001 | 0.0437 | 0.166 |
| 36 | 10 | 0.756 | 0.001 | 0.0425 | 0.167 |
| 36 | 10 | 0.757 | 0.001 | 0.0432 | 0.165 |
| 36 | 10 | 0.758 | 0.001 | 0.042 | 0.161 |
| 36 | 10 | 0.759 | 0.001 | 0.04 | 0.166 |
| 36 | 10 | 0.76 | 0.001 | 0.0403 | 0.163 |
| 36 | 10 | 0.761 | 0.001 | 0.039 | 0.164 |
| 36 | 10 | 0.762 | 0.001 | 0.043 | 0.156 |
| 36 | 10 | 0.763 | 0.001 | 0.043 | 0.155 |
| 36 | 10 | 0.764 | 0.001 | 0.045 | 0.16 |
| 36 | 10 | 0.765 | 0.001 | 0.0405 | 0.165 |
| 36 | 10 | 0.766 | 0.001 | 0.0403 | 0.162 |
| 36 | 10 | 0.767 | 0.001 | 0.0408 | 0.147 |
| 36 | 10 | 0.768 | 0.001 | 0.0442 | 0.163 |
| 36 | 10 | 0.769 | 0.001 | 0.0398 | 0.164 |
| 36 | 10 | 0.77 | 0.001 | 0.046 | 0.157 |
| 36 | 10 | 0.771 | 0.001 | 0.04 | 0.165 |
| 36 | 10 | 0.772 | 0.001 | 0.0478 | 0.163 |
| 36 | 10 | 0.773 | 0.001 | 0.0403 | 0.168 |
| 36 | 10 | 0.774 | 0.001 | 0.0442 | 0.172 |
| 36 | 10 | 0.775 | 0.001 | 0.045 | 0.167 |
| 36 | 10 | 0.776 | 0.001 | 0.0372 | 0.172 |
| 36 | 10 | 0.777 | 0.001 | 0.046 | 0.157 |
| 36 | 10 | 0.778 | 0.001 | 0.04 | 0.17 |
| 36 | 10 | 0.779 | 0.001 | 0.0403 | 0.17 |
| 36 | 10 | 0.78 | 0.001 | 0.0425 | 0.16 |
| 36 | 10 | 0.781 | 0.001 | 0.0415 | 0.161 |
| 36 | 10 | 0.782 | 0.001 | 0.0472 | 0.166 |
| 36 | 10 | 0.783 | 0.001 | 0.039 | 0.161 |
| 36 | 10 | 0.784 | 0.001 | 0.04 | 0.17 |
| 36 | 10 | 0.785 | 0.001 | 0.042 | 0.167 |
| 36 | 10 | 0.786 | 0.001 | 0.0465 | 0.158 |
| 36 | 10 | 0.787 | 0.001 | 0.044 | 0.17 |
| 36 | 10 | 0.788 | 0.001 | 0.0375 | 0.155 |
| 36 | 10 | 0.789 | 0.001 | 0.0435 | 0.162 |
| 36 | 10 | 0.79 | 0.001 | 0.0398 | 0.163 |
| 36 | 10 | 0.791 | 0.001 | 0.0418 | 0.158 |
| 36 | 10 | 0.792 | 0.001 | 0.0367 | 0.159 |
| 36 | 10 | 0.793 | 0.001 | 0.0385 | 0.158 |
| 36 | 10 | 0.794 | 0.001 | 0.0478 | 0.173 |
| 36 | 10 | 0.795 | 0.001 | 0.043 | 0.165 |
| 36 | 10 | 0.796 | 0.001 | 0.0357 | 0.158 |
| 36 | 10 | 0.797 | 0.001 | 0.0428 | 0.168 |
| 36 | 10 | 0.798 | 0.001 | 0.044 | 0.166 |
| 36 | 10 | 0.799 | 0.001 | 0.0415 | 0.157 |
| 36 | 10 | 0.8 | 0.001 | 0.0398 | 0.161 |
| 36 | 10 | 0.801 | 0.001 | 0.041 | 0.158 |
| 36 | 10 | 0.802 | 0.001 | 0.038 | 0.162 |
| 36 | 10 | 0.803 | 0.001 | 0.0465 | 0.165 |
| 36 | 10 | 0.804 | 0.001 | 0.0428 | 0.169 |
| 36 | 10 | 0.805 | 0.001 | 0.04 | 0.164 |
| 36 | 10 | 0.806 | 0.001 | 0.0403 | 0.164 |
| 36 | 10 | 0.807 | 0.001 | 0.041 | 0.158 |
| 36 | 10 | 0.808 | 0.001 | 0.0395 | 0.169 |
| 36 | 10 | 0.809 | 0.001 | 0.0493 | 0.159 |
| 36 | 10 | 0.81 | 0.001 | 0.0442 | 0.171 |
| 36 | 10 | 0.811 | 0.001 | 0.043 | 0.166 |
| 36 | 10 | 0.812 | 0.001 | 0.0385 | 0.165 |
| 36 | 10 | 0.813 | 0.001 | 0.0372 | 0.167 |
| 36 | 10 | 0.814 | 0.001 | 0.0418 | 0.152 |
| 36 | 10 | 0.815 | 0.001 | 0.0465 | 0.16 |
| 36 | 10 | 0.816 | 0.001 | 0.0405 | 0.165 |
| 36 | 10 | 0.817 | 0.001 | 0.0423 | 0.166 |
| 36 | 10 | 0.818 | 0.001 | 0.0445 | 0.166 |
| 36 | 10 | 0.819 | 0.001 | 0.0385 | 0.164 |
| 36 | 10 | 0.82 | 0.001 | 0.0447 | 0.163 |
| 36 | 10 | 0.821 | 0.001 | 0.042 | 0.165 |
| 36 | 10 | 0.822 | 0.001 | 0.0442 | 0.162 |
| 36 | 10 | 0.823 | 0.001 | 0.0405 | 0.167 |
| 36 | 10 | 0.824 | 0.001 | 0.0428 | 0.165 |
| 36 | 10 | 0.825 | 0.001 | 0.0428 | 0.174 |
| 36 | 10 | 0.826 | 0.001 | 0.0403 | 0.161 |
| 36 | 10 | 0.827 | 0.001 | 0.0387 | 0.161 |
| 36 | 10 | 0.828 | 0.001 | 0.0445 | 0.165 |
| 36 | 10 | 0.829 | 0.001 | 0.0382 | 0.164 |
| 36 | 10 | 0.83 | 0.001 | 0.0408 | 0.16 |
| 36 | 10 | 0.831 | 0.001 | 0.0442 | 0.156 |
| 36 | 10 | 0.832 | 0.001 | 0.046 | 0.166 |
| 36 | 10 | 0.833 | 0.001 | 0.0377 | 0.16 |
| 36 | 10 | 0.834 | 0.001 | 0.0398 | 0.16 |
| 36 | 10 | 0.835 | 0.001 | 0.0435 | 0.167 |
| 36 | 10 | 0.836 | 0.001 | 0.046 | 0.162 |
| 36 | 10 | 0.837 | 0.001 | 0.0445 | 0.167 |
| 36 | 10 | 0.838 | 0.001 | 0.0467 | 0.176 |
| 36 | 10 | 0.839 | 0.001 | 0.0442 | 0.146 |
| 36 | 10 | 0.84 | 0.001 | 0.04 | 0.168 |
| 36 | 10 | 0.841 | 0.001 | 0.0423 | 0.165 |
| 36 | 10 | 0.842 | 0.001 | 0.042 | 0.155 |
| 36 | 10 | 0.843 | 0.001 | 0.0428 | 0.162 |
| 36 | 10 | 0.844 | 0.001 | 0.04 | 0.17 |
| 36 | 10 | 0.845 | 0.001 | 0.0452 | 0.156 |
| 36 | 10 | 0.846 | 0.001 | 0.0452 | 0.157 |
| 36 | 10 | 0.847 | 0.001 | 0.0392 | 0.17 |
| 36 | 10 | 0.848 | 0.001 | 0.0465 | 0.178 |
| 36 | 10 | 0.849 | 0.001 | 0.0357 | 0.16 |
| 36 | 10 | 0.85 | 0.001 | 0.0387 | 0.163 |
| 36 | 10 | 0.851 | 0.001 | 0.0382 | 0.163 |
| 36 | 10 | 0.852 | 0.001 | 0.0425 | 0.16 |
| 36 | 10 | 0.853 | 0.001 | 0.0435 | 0.166 |
| 36 | 10 | 0.854 | 0.001 | 0.0442 | 0.16 |
| 36 | 10 | 0.855 | 0.001 | 0.0432 | 0.17 |
| 36 | 10 | 0.856 | 0.001 | 0.0432 | 0.169 |
| 36 | 10 | 0.857 | 0.001 | 0.0437 | 0.164 |
| 36 | 10 | 0.858 | 0.001 | 0.0395 | 0.162 |
| 36 | 10 | 0.859 | 0.001 | 0.0428 | 0.154 |
| 36 | 10 | 0.86 | 0.001 | 0.041 | 0.168 |
| 36 | 10 | 0.861 | 0.001 | 0.0408 | 0.154 |
| 36 | 10 | 0.862 | 0.001 | 0.0408 | 0.169 |
| 36 | 10 | 0.863 | 0.001 | 0.0413 | 0.163 |
| 36 | 10 | 0.864 | 0.001 | 0.0435 | 0.168 |
| 36 | 10 | 0.865 | 0.001 | 0.0467 | 0.168 |
| 36 | 10 | 0.866 | 0.001 | 0.0403 | 0.169 |
| 36 | 10 | 0.867 | 0.001 | 0.0385 | 0.169 |
| 36 | 10 | 0.868 | 0.001 | 0.0432 | 0.167 |
| 36 | 10 | 0.869 | 0.001 | 0.041 | 0.161 |
| 36 | 10 | 0.87 | 0.001 | 0.0425 | 0.16 |
| 36 | 10 | 0.871 | 0.001 | 0.0405 | 0.166 |
| 36 | 10 | 0.872 | 0.001 | 0.0395 | 0.155 |
| 36 | 10 | 0.873 | 0.001 | 0.0423 | 0.175 |
| 36 | 10 | 0.874 | 0.001 | 0.0442 | 0.169 |
| 36 | 10 | 0.875 | 0.001 | 0.0485 | 0.168 |
| 36 | 10 | 0.876 | 0.001 | 0.0357 | 0.172 |
| 36 | 10 | 0.877 | 0.001 | 0.0398 | 0.154 |
| 36 | 10 | 0.878 | 0.001 | 0.0432 | 0.171 |
| 36 | 10 | 0.879 | 0.001 | 0.0405 | 0.166 |
| 36 | 10 | 0.88 | 0.001 | 0.0425 | 0.168 |
| 36 | 10 | 0.881 | 0.001 | 0.0457 | 0.165 |
| 36 | 10 | 0.882 | 0.001 | 0.0432 | 0.161 |
| 36 | 10 | 0.883 | 0.001 | 0.0372 | 0.153 |
| 36 | 10 | 0.884 | 0.001 | 0.0452 | 0.158 |
| 36 | 10 | 0.885 | 0.001 | 0.043 | 0.168 |
| 36 | 10 | 0.886 | 0.001 | 0.0425 | 0.162 |
| 36 | 10 | 0.887 | 0.001 | 0.0333 | 0.17 |
| 36 | 10 | 0.888 | 0.001 | 0.04 | 0.175 |
| 36 | 10 | 0.889 | 0.001 | 0.0423 | 0.166 |
| 36 | 10 | 0.89 | 0.001 | 0.042 | 0.165 |
| 36 | 10 | 0.891 | 0.001 | 0.044 | 0.157 |
| 36 | 10 | 0.892 | 0.001 | 0.0437 | 0.168 |
| 36 | 10 | 0.893 | 0.001 | 0.0415 | 0.167 |
| 36 | 10 | 0.894 | 0.001 | 0.0387 | 0.153 |
| 36 | 10 | 0.895 | 0.001 | 0.046 | 0.165 |
| 36 | 10 | 0.896 | 0.001 | 0.0457 | 0.157 |
| 36 | 10 | 0.897 | 0.001 | 0.0425 | 0.156 |
| 36 | 10 | 0.898 | 0.001 | 0.0403 | 0.17 |
| 36 | 10 | 0.899 | 0.001 | 0.0423 | 0.161 |
| 36 | 10 | 0.9 | 0.001 | 0.0418 | 0.164 |
| 36 | 10 | 0.901 | 0.001 | 0.0415 | 0.171 |
| 36 | 10 | 0.902 | 0.001 | 0.0372 | 0.165 |
| 36 | 10 | 0.903 | 0.001 | 0.0472 | 0.154 |
| 36 | 10 | 0.904 | 0.001 | 0.0432 | 0.162 |
| 36 | 10 | 0.905 | 0.001 | 0.045 | 0.166 |
| 36 | 10 | 0.906 | 0.001 | 0.0395 | 0.169 |
| 36 | 10 | 0.907 | 0.001 | 0.0435 | 0.164 |
| 36 | 10 | 0.908 | 0.001 | 0.0415 | 0.162 |
| 36 | 10 | 0.909 | 0.001 | 0.041 | 0.167 |
| 36 | 10 | 0.91 | 0.001 | 0.0423 | 0.161 |
| 36 | 10 | 0.911 | 0.001 | 0.0442 | 0.17 |
| 36 | 10 | 0.912 | 0.001 | 0.044 | 0.167 |
| 36 | 10 | 0.913 | 0.001 | 0.0408 | 0.162 |
| 36 | 10 | 0.914 | 0.001 | 0.0395 | 0.167 |
| 36 | 10 | 0.915 | 0.001 | 0.0415 | 0.167 |
| 36 | 10 | 0.916 | 0.001 | 0.05 | 0.174 |
| 36 | 10 | 0.917 | 0.001 | 0.0425 | 0.157 |
| 36 | 10 | 0.918 | 0.001 | 0.0375 | 0.165 |
| 36 | 10 | 0.919 | 0.001 | 0.047 | 0.165 |
| 36 | 10 | 0.92 | 0.001 | 0.0408 | 0.17 |
| 36 | 10 | 0.921 | 0.001 | 0.0423 | 0.161 |
| 36 | 10 | 0.922 | 0.001 | 0.0442 | 0.151 |
| 36 | 10 | 0.923 | 0.001 | 0.0415 | 0.169 |
| 36 | 10 | 0.924 | 0.001 | 0.0385 | 0.174 |
| 36 | 10 | 0.925 | 0.001 | 0.0413 | 0.171 |
| 36 | 10 | 0.926 | 0.001 | 0.0377 | 0.161 |
| 36 | 10 | 0.927 | 0.001 | 0.0387 | 0.16 |
| 36 | 10 | 0.928 | 0.001 | 0.043 | 0.165 |
| 36 | 10 | 0.929 | 0.001 | 0.0423 | 0.158 |
| 36 | 10 | 0.93 | 0.001 | 0.0465 | 0.156 |
| 36 | 10 | 0.931 | 0.001 | 0.0437 | 0.157 |
| 36 | 10 | 0.932 | 0.001 | 0.0377 | 0.17 |
| 36 | 10 | 0.933 | 0.001 | 0.0452 | 0.164 |
| 36 | 10 | 0.934 | 0.001 | 0.048 | 0.154 |
| 36 | 10 | 0.935 | 0.001 | 0.0472 | 0.171 |
| 36 | 10 | 0.936 | 0.001 | 0.0485 | 0.165 |
| 36 | 10 | 0.937 | 0.001 | 0.0415 | 0.159 |
| 36 | 10 | 0.938 | 0.001 | 0.0408 | 0.18 |
| 36 | 10 | 0.939 | 0.001 | 0.042 | 0.166 |
| 36 | 10 | 0.94 | 0.001 | 0.0377 | 0.16 |
| 36 | 10 | 0.941 | 0.001 | 0.0445 | 0.165 |
| 36 | 10 | 0.942 | 0.001 | 0.0437 | 0.163 |
| 36 | 10 | 0.943 | 0.001 | 0.047 | 0.174 |
| 36 | 10 | 0.944 | 0.001 | 0.04 | 0.17 |
| 36 | 10 | 0.945 | 0.001 | 0.0437 | 0.163 |
| 36 | 10 | 0.946 | 0.001 | 0.043 | 0.171 |
| 36 | 10 | 0.947 | 0.001 | 0.04 | 0.17 |
| 36 | 10 | 0.948 | 0.001 | 0.0445 | 0.164 |
| 36 | 10 | 0.949 | 0.001 | 0.0445 | 0.171 |
| 36 | 10 | 0.95 | 0.001 | 0.0418 | 0.151 |

# 6 Reference

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