Problem set

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Problem 1

Question a

To calculate a sample size, we need additional information including:

1) The dependent variable is approximately normally distributed within each group.

2) The data is collected from a representative, randomly selected portion of the total population.

3) Sample sizes of two groups.

Question b

If we assume sample size of two groups are the same and assumption 1) and 2) are valid. As $t = \frac{d}{var \times \sqrt{\frac{2}{n}}}$ In order to have 5% significance, $t > t_{1-\frac{2}{\alpha},2n-2}$

```
d = 10
var = 20
n = 2
t = d/(var*sqrt(2/n))
while (t<=qt(0.975, 2*n-2)) {
  n = n+1
  t = d/(var*sqrt(2/n))
}
n

## [1] 32
```

The sample size is 32.

Problem 2

Question a

```
14*pbinom(0, 14, 0.05) + 34*(1-pbinom(0, 14, 0.05))

## [1] 24.2465
```

The expected value of the sample size is around 24.25.

Question b

Let R_i be the number of responses in the first or second stages, where $i \in \{1,2\}$.

The probability of a "go" decision is

$$\begin{aligned} P_b &= \sum_{j=1}^{4} [P(R_1 + R_2 \geq 4)] + P(R_1 > 4) \\ &= \sum_{j=1}^{4} [P(R_2 > 3 - j, R_1 = j)] + P(R_1 > 4) \\ &= \sum_{j=1}^{4} [P(R_2 > 3 - j)P(R_1 = j)] + P(R_1 > 4) \end{aligned}$$

.

```
pbinom(2, 20, 0.05, lower.tail = FALSE)*dbinom(1, 14, 0.05) + pbinom(1, 20,
0.05, lower.tail = FALSE)*dbinom(2, 14, 0.05) + pbinom(0, 20, 0.05,
lower.tail = FALSE)*dbinom(3, 14, 0.05) + pbinom(3, 14, 0.05, lower.tail =
FALSE)

## [1] 0.0803739
```

So the probability of a "go" decision is around 0.080.

Question c

```
pbinom(2, 20, 0.2, lower.tail = FALSE)*dbinom(1, 14, 0.2) + pbinom(1, 20,
0.2, lower.tail = FALSE)*dbinom(2, 14, 0.2) + pbinom(0, 20, 0.2, lower.tail =
FALSE)*dbinom(3, 14, 0.2) + pbinom(3, 14, 0.2, lower.tail = FALSE)

## [1] 0.9041092
```

When the true response rate is 20%, the probability of a "go" decision is around 0.904.

Question d

Let n be the sample size of the fixed design, R be the number of response in the trial, if there is at least x response, then the treatment is deemed promising ("go")

$$type\ I\ error = P(reject\ null|null\ is\ true) = P(R > X|p = 0.05)$$

$$power = P(reject\ null|alternative\ is\ true) = P(R > X|p = 0.2)$$

```
n = 3
x = 1
while(pbinom(x-1,n,0.05,lower.tail = FALSE)>0.080 | pbinom(x-
1,n,0.2,lower.tail = FALSE)<0.904){
  if(x<n-1){
    x = x+1
```

```
  } else {
    x = 1
    n = n+1}
}
n

## [1] 32
```

The sample size required for a fixed design with null response 5% and alternative response 20% is 32.

Problem 3

Question a

Assume, $\lambda \sim \Gamma(\alpha, \beta), f(\lambda|\alpha, \beta) = \frac{\beta^\alpha \lambda^{\alpha-1} e^{-\beta\lambda}}{\Gamma(\alpha)}$, for $\lambda > 0$.

$$
\begin{aligned}
f(x) &= \int_0^{+\infty} f\,(x|\lambda) f(\lambda) d\lambda \\
&= \int_0^{+\infty} \lambda\, e^{-\lambda x} \frac{\beta^\alpha \lambda^{\alpha-1} e^{-\beta\lambda}}{\Gamma(\alpha)} d\lambda \\
&= \int_0^{+\infty} \frac{\lambda^\alpha \beta^\alpha e^{-(\beta+x)\lambda}}{\Gamma(\alpha)} d\lambda \\
&= \int_0^{+\infty} \frac{\lambda^{(\alpha+1)-1} (\beta+x)^{\alpha+1} e^{-(\beta+x)\lambda}}{\Gamma(\alpha+1)} \frac{\beta^\alpha (\alpha+1)}{(\beta+x)^{\alpha+1}} d\lambda \\
&= \frac{\beta^\alpha (\alpha+1)}{(\beta+x)^{\alpha+1}}
\end{aligned}
$$

Posterior Distribution:

$$
\begin{aligned}
f(\lambda|x) &= \frac{f(x_1|\lambda) f(\lambda)}{f(x_1)} \\
&= \frac{\lambda e^{-\lambda x_1} \frac{\beta^\alpha \lambda^{\alpha-1} e^{-\beta\lambda}}{\Gamma(\alpha)}}{\frac{\beta^\alpha (\alpha+1)}{(\beta+x_1)^{\alpha+1}}} \\
&= \frac{\lambda e^{-\lambda x_1} \lambda^{\alpha-1} e^{-\beta\lambda} (\beta+x_1)^{\alpha+1}}{\Gamma(\alpha+1)} \\
&= \frac{e^{-\lambda(x_1+\beta)} \lambda^\alpha (\beta+x_1)^{\alpha+1}}{\Gamma(\alpha+1)} \\
&= \Gamma(\alpha+1, \beta+x)
\end{aligned}
$$

Question b

$$
\begin{aligned}
f(x_2|x_1) &= \frac{f(x_1,x_2)}{f(x_1)} = \frac{\int_0^{+\infty} f(x_1|\lambda)f(x_2|\lambda)f(\lambda)d\lambda}{f(x_1)} \\
&= \frac{\int_0^{+\infty} \lambda e^{-\lambda x_1}\lambda e^{-\lambda x_2}\frac{\beta^\alpha \lambda^{\alpha-1}e^{-\beta\lambda}}{\Gamma(\alpha)}d\lambda}{\frac{\beta^\alpha(\alpha+1)}{(\beta+x_1)^{\alpha+1}}} \\
&= \int_0^{+\infty} \frac{\lambda^{\alpha+1}e^{-\lambda(x_1+x_2+\beta)}(\beta+x_1)^{\alpha+1}}{\Gamma(\alpha+1)}d\lambda \\
&= \int_0^{+\infty} \frac{\lambda^{\alpha+1}e^{-\lambda(x_1+x_2+\beta)}(\beta+x_1+x_2)^{\alpha+2}}{\Gamma(\alpha+2)}\frac{(\beta+x_1)^{\alpha+1}(\alpha+2)}{(\beta+x_1+x_2)^{\alpha+2}}d\lambda \\
&= \frac{(\beta+x_1)^{\alpha+1}(\alpha+2)}{(\beta+x_1+x_2)^{\alpha+2}}
\end{aligned}
$$

Question c

$$
\begin{cases}
Y_1 &= \dfrac{X_1+X_2}{2} \\
Y_2 &= X_1
\end{cases}
$$

$$
J = \begin{vmatrix} \frac{\partial Y_1}{\partial X_1} & \frac{\partial Y_1}{\partial X_2} \\ \frac{\partial Y_2}{\partial X_1} & \frac{\partial Y_2}{\partial X_2} \end{vmatrix} = \begin{vmatrix} 1/2 & 1/2 \\ 1 & 0 \end{vmatrix} = -1/2
$$

$$
\begin{aligned}
f(\frac{x_1+x_2}{2}|x_1) &= \frac{f(\frac{x_1+x_2}{2},x_1)}{f(x_1)} = \frac{f(y_1,y_2)}{f(x_1)} = -\frac{f(x_1,x_2)}{2f(x_1)} \\
&= -\frac{(\beta+x_1)^{\alpha+1}(\alpha+2)}{2(\beta+x_1+x_2)^{\alpha+2}}
\end{aligned}
$$

Problem 4

Dose level 1 is safe:

1.number of DLT equals to 0 or

2.number of DLT equals to 1 and numbers of DLT equals to 0 for another 3 patients at same level.

```
dbinom(0,3,0.25)+dbinom(1,3,0.25)*dbinom(0,3,0.25)

## [1] 0.5998535
```

The probaility that the 3+3 algorithm declare dose level 1 is safe is 0.600.

Problem 5

Question a

Dose 1: 0.007 0.135 0.772 < 0.02 1/3 | 0.444 0.287 0.347 < 0.02 0/3

Dose 2: 0.777 0.604 0.025 < 0.04 1/3 | 0.584 0.715 0.110 < 0.04 0/3

Dose 3: 0.770 0.405 0.742 < 0.1 0/3

Dose 4: 0.923 0.591 0.567 < 0.25 0/3

Dose 5: 0.952 0.039 0.342 < 0.5 2/3

MTD = 4

Question b

- Trial 1

Dose 1: 0.534 0.342 0.661 < 0.02 0/3

Dose 2: 0.829 0.489 0.710 < 0.04 0/3

Dose 3: 0.921 0.055 0.497 < 0.1 1/3 | 0.611 0.118 0.122 < 0.1 0/3

Dose 4: 0.472 0.853 0.931 < 0.25 0/3

Dose 5: 0.978 0.232 0.519 < 0.5 1/3 | 0.333 0.096 0.709 < 0.5 2/3

MTD = 4

- Trial 2

Dose 1: 0.985 0.844 0.948 < 0.02 0/3

Dose 2: 0.361 0.061 0.541 < 0.04 0/3

Dose 3: 0.815 0.153 0.177 < 0.1 0/3

Dose 4: 0.495 0.735 0.872 < 0.25 0/3

Dose 5: 0.799 0.028 0.555 < 0.5 1/3 | 0.763 0.752 0.682 < 0.5 0/3

MTD = 5

- Trial 3

Dose 1: 0.228 0.586 0.732 < 0.01 0/3

Dose 2: 0.014 0.753 0.412 < 0.04 1/3 | 0.765 0.176 0.919 < 0.04 0/3

Dose 3: 0.207 0.874 0.178 < 0.1 0/3

Dose 4: 0.820 0.783 0.231 < 0.25 1/3 | 0.541 0.925 0.207 < 0.25 1/3

MTD = 3

- Trial 4

Dose 1: 0.408 0.808 0.434 < 0.02 0/3

Does 2: 0.008 0.382 0.166 < 0.04 1/3 | 0.328 0.294 0.635 < 0.04 0/3

Dose 3: 0.672 0.669 0.460 < 0.1 0/3

Dose 4: 0.174 0.374 0.381 < 0.25 1/3 | 0.600 0.397 0.091 < 0.25 1/3

MTD = 3

- Trial 5

Dose 1: 0.922 0.872 0.754 < 0.02 0/3

Dose 2: 0.520 0.977 0.748 <0.04 0/3

Dose 3: 0.955 0.978 0.531 < 0.1 0/3

Dose 4: 0.196 0.963 0.356 <0.25 1/3 | 0.061 0.795 0.823 < 0.25 1/3

MTD = 3

- Trial 6

Dose 1: 0.731 0.284 0.929 <0.02 0/3

Dose 2: 0.687 0.858 0.439 <0.04 0/3

Dose 3: 0.944 0.676 0.189 < 0.1 0/3

Dose 4: 0.755 0.421 0.357 <0.25 0/3

Dose 5: 0.391 0.370 0.028 <0.5 3/3

MTD = 4

- Trial 7

Dose 1: 0.866 0.069 0.818 < 0.02 0/3

Dose 2: 0.888 0.381 0.989 < 0.04 0/3

Dose 3: 0.663 0.491 0.285 < 0.1 0/3

Dose 4: 0.000 0.652 0.341 < 0.25 1/3 | 0.316 0.599 0.977 < 0.25 0/3

Dose 5: 0.332 0.985 0.976 < 0.5 1/3 | 0.695 0.730 0.580 < 0.5 0/3

MTD = 5

- Trial 8

Dose 1: 0.562 0.674 0.435 < 0.02 0/3

Dose 2: 0.747 0.521 0.024 < 0.04 1/3 | 0.412 0.719 0.819 <0.04 0/3

Dose 3: 0.139 0.278 0.270 < 0.1 0/3

Dose 4: 0.877 0.431 0.867 < 0.25 0/3

Dose 5: 0.723 0.919 0.244 <0.5 1/3 | 0.362 0.442 0.196 <0.5 3/3

MTD = 4

- Trial 9

Dose 1: 0.409 0.752 0.351 <0.02 0/3

Dose 2: 0.979 0.189 0.523 <0.04 0/3

Dose 3: 0.332 0.690 0.061 <0.1 1/3 | 0.552 0.253 0.450 <0.1 0/3

Dose 4: 0.403 0.592 0.381 <0.25 0/3

Dose 5:

0.673 0.182 0.862 <0.5 1/3 | 0.223 0.090 0.729 <0.5 2/3

MTD = 4

- Trial 10

Dose 1 0.091 0.315 0.763 <0.02 0/3

Dose 2 0.373 0.174 0.927 < 0.04 0/3

Dose 3 0.264 0.799 0.653 <0.1 0/3

Dose 4 0.569 0.109 0.706 <0.25 1/3 | 0.858 0.357 0.950 <0.25 0/3

Dose 5 0.801 0.123 0.019 <0.5 2/3

MTD = 4

```r
data.frame(Dose = 0:5, probability = c(0,0,0,3,5,2)/10)
```

```
##   Dose probability
## 1    0         0.0
## 2    1         0.0
## 3    2         0.0
## 4    3         0.3
## 5    4         0.5
## 6    5         0.2
```

Problem 6

```r
library(dfcrm)
target = 0.1
prior = c(0.05, 0.12, 0.25, 0.40, 0.55)
trueP = c(0.02, 0.04, 0.10, 0.25, 0.50)
N = 20
crmoutput = crmsim(trueP, prior, target, N, 3, model = "logistic")
crmoutput$MTD

## [1] 2
```

Problem 7

```r
crmoutput = crmsim(trueP, prior, target, N, 3, nsim = 10, model = "logistic")

## simulation number: 1
## simulation number: 2
## simulation number: 3
## simulation number: 4
## simulation number: 5
## simulation number: 6
## simulation number: 7
## simulation number: 8
## simulation number: 9
## simulation number: 10

data.frame(dose = 1: 5, probability = crmoutput$MTD)

##   dose probability
## 1    1         0.0
## 2    2         0.1
## 3    3         0.6
## 4    4         0.3
## 5    5         0.0
```

Problem 8

Assume $\lambda_1 \sim \Gamma(\alpha_1, \beta_1), \lambda_2 \sim \Gamma(\alpha_2, \beta_2)$

$$Pr(\lambda_1 > \lambda_2 | x_1, \ldots, x_n, y_1, \ldots, y_m) = Pr((\lambda_1 | x_1, \ldots, x_n) > (\lambda_2 | y_1, \ldots, y_m))$$

where

$$\lambda_1 | x_1, \ldots, x_n \sim \Gamma(\alpha_1 + n, \beta_1 + \sum_{i=1}^{n} x_i), \lambda_2 | y_1, \ldots, y_m \ \Gamma(\alpha_2 + m, \beta_2 + \sum_{j=1}^{m} y_j)$$

Given $\alpha_1, \alpha_2, \beta_1, \beta_2, n, m, \sum_{i=1}^{n} x_i, \sum_{j=1}^{m} y_j$, we can simulate 1000 λ_1 and λ_2 and calculate $Pr(\lambda_1 > \lambda_2 | x_1, \ldots, x_n, y_1, \ldots, y_m)$.

$$Pr(\lambda_1 > \lambda_2 | x_1, \dots, x_n, y_1, \dots, y_m)$$
$$= \int_0^{\infty} \int_0^{\lambda_1} \Gamma\,(\alpha_1 + n, \beta_1 + \sum_{i=1}^{n} x_i)\Gamma(\alpha_2 + m, \beta_2 + \sum_{j=1}^{m} y_j) d\lambda_2 d\lambda_1$$

Problem 9

Question a

$$f(\mu|x_1,\dots,x_n) = \frac{f(x_1,\dots,x_n|\mu)}{f(x_1,\dots,x_n)}.$$
$$\propto f(x_1|\mu)f(x_2|\mu)\cdots f(\mu).$$
$$\propto \prod_{i=1}^{n} \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{(x_i-\mu)^2}{2}\right)\cdot \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{\mu^2}{2}\right).$$
$$\propto \exp\left(-\sum_{i=1}^{n} \frac{x_i-2\mu x_i+\mu^2}{2}-\frac{\mu^2}{2}\right)$$
$$\propto \exp\left[\cancel{\pm\frac{\mu^2-2\mu\bar{x}}{2}} - \frac{n}{2}(-2\mu\bar{x}+\mu^2)-\frac{\mu^2}{2}\right]\cdot \exp\left(-\sum_{i=1}^{n}\frac{x_i^2}{2}\right)$$
$$\propto \exp\left(n\mu\bar{x} - \frac{n\mu^2}{2} - \frac{\mu^2}{2}\right).$$
$$\propto \exp\left(-\frac{1}{2}[(n+1)\mu^2-2n\mu\bar{x}]\right)$$
$$\propto \exp\left[-\frac{(\mu-\frac{n}{n+1}\bar{x})^2}{2(\frac{1}{n+1})}\right]^2$$
So $\mu|x_1, x_2 \dots x_n \sim N(\frac{n}{n+1}\bar{x}, \frac{1}{n+1})$ where $\bar{x}=\frac{1}{n}\sum_{i=1}^{n} x_i$

Problem 9 Question a.

Question b

According to Question a, $v|y_1, \dots, y_m \sim N(\frac{m}{m+1}\bar{y}, \frac{1}{m+1})$ where $\bar{y} = \frac{1}{n}\sum_{i=1}^{n} y_i$

As x_i and y_i are independent

$$Pr(\mu > v|x_1, \dots, x_n, y_1, \dots, y_m) = \int_{-\infty}^{+\infty} \int_{-\infty}^{\mu} f\,(\mu, v|x_1, \dots, x_n, y_1, \dots, y_m)$$

$$= \int_{-\infty}^{+\infty} \int_{-\infty}^{\mu} f\,(\mu|x_1, \dots, x_m) f(v|y_1, \dots, y_m)$$

$$= \int_{-\infty}^{+\infty} \int_{-\infty}^{\mu} \frac{1}{\sqrt{\frac{4\pi^2}{(n+1)(m+1)}}} exp(-\frac{(\mu - \frac{n}{n+1}\overline{x})^2}{\frac{2}{n+1}} - \frac{v - \frac{m}{m+1}\overline{y})^2}{\frac{2}{m+1}}) dv d\mu$$

Problem 10

Question a

$$L(\alpha, \beta, \sigma^2|x_i, y_i, i = 1,2, \dots, n) = \prod_{i=1}^{n} \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(y_i - (\alpha + \beta x_i))^2}{2\sigma^2}}$$

$$l(\alpha, \beta, \sigma^2|x_i, y_i, i = 1,2, \dots, n) = -\frac{n}{2} log(2\pi) - nlog\sigma - \frac{1}{2\sigma^2} \sum_{i=1}^{n} (y_i - (\alpha + \beta x_i))^2$$

$$\hat{\beta} = \frac{\sum_{i=1}^{n}(x_i - \overline{x})(y_i - \overline{y})}{\sum_{i=1}^{n}(x_i - \overline{x})^2}$$

$$\hat{\alpha} = \overline{y} - \hat{\beta}\overline{x}$$

$$\hat{\sigma}^2 = \frac{1}{n} \sum_{i=1}^{n} (y_i - (\hat{\alpha} + \hat{\beta} x_i))^2$$

Question b

$f(\alpha,\beta|y_1\dots y_n) \propto [\prod_{i=1}^{n} f(y_i|x_i,\alpha,\beta,\sigma^2)]\, f(\alpha,\beta)$

$\cancel{\propto [\prod_{i=1}^{n} (\frac{1}{\sigma}\exp(-\frac{(y_i-(\alpha+\beta x_i))^2}{2\sigma^2})) \times \dots]}$

$\cancel{\propto [\frac{1}{\sigma^n}} \propto \prod_{i=1}^{n} (\frac{1}{\sigma}\exp(-\frac{(y_i-(\alpha+\beta x_i))^2}{2\sigma^2})) \times 1$

$\propto \frac{1}{\sigma^n}\exp(-\frac{\Sigma(y_i-(\alpha+\beta x_i))^2}{2\sigma^2})$

$\propto \frac{1}{\sqrt{2\pi}\sigma}\exp(-\frac{\Sigma(y_i-(\alpha+\beta x_i))^2}{2\sigma^2})$

So $(\alpha,\beta)^T|\sigma^2$ Data $\sim$ Bivariate Normal $(\begin{pmatrix}\alpha_0\\ \beta_0\end{pmatrix}, \sigma^2\Sigma_0)$

where $\Sigma_0 = \sigma^2\begin{pmatrix} S_\alpha & S_{\alpha\beta}\\ S_{\alpha\beta} & S_\beta\end{pmatrix}$ and $\alpha|\sigma^2 \sim N(\alpha_0,\sigma^2 S_\alpha)$

$\beta|\sigma^2 \sim N(\beta_0,\sigma^2 S_\beta$

Question c

Let $\phi = \frac{1}{\sigma^2}$

$f(\phi) = f(\frac{1}{\sigma^2}) = \frac{b^a}{\Gamma(a)}\phi^{a-1}e^{-b\phi}$

$f(\phi|\alpha,\beta,y_1\dots y_n) \propto f(\alpha,\beta,y_1\dots y_n|\phi)\, f(\phi)$

$\propto \prod_{i=1}^{n}\frac{1}{\sqrt{\frac{2\pi}{\phi}}}\exp(\frac{-\phi(y_i-(\alpha+\beta x_i))^2}{2})\cdot\frac{b^a}{\Gamma(a)}\phi^{a-1}e^{-b\phi}$

$\propto \phi^{\frac{n}{2}+a-1}\exp(-(\frac{\Sigma(y_i-\alpha+\beta x_i))^2}{2}+b)\phi)$

So ϕ | Data $\sim$ Gama $(\frac{n}{2}+a, \frac{\Sigma(y_i-(\alpha+\beta x_i))^2}{2}+b)$

~~R~~ conjugate prior $\sigma^2 \sim$ Gamma(a,b)

Problem 10 Question b&c.

d) According to b), c)

$$f(\alpha,\beta,\phi \mid y_1 \dots y_n) \propto f(y_1 \dots y_n \mid \alpha,\beta,\phi) f(\alpha,\beta,\phi)$$

$$\propto f(y_1 \dots y_n \mid \alpha,\beta,\phi) f(\alpha,\beta) f(\phi)$$

$$\propto \phi^{\frac{n}{2}-1} \exp\left(-\frac{\Sigma(y_i-(\alpha+\beta x_i))^2}{2}\phi\right)$$

$$\frac{\partial f(\alpha,\beta,\phi \mid y_1 \dots y_n)}{\partial \alpha} = f(\beta,\phi \mid y_1 \dots y_n)$$

$$= \int_{-\infty}^{+\infty} (\alpha,\beta,\phi \mid y_1 \dots y_n)\, d\alpha.$$

$$\cancel{= \phi^{\frac{n}{2}-1} \phi f(}$$

$$= \int_{-\infty}^{+\infty} \phi^{\frac{n}{2}-1} \exp\left(-\frac{\Sigma(y_i-(\alpha+\beta x_i))^2}{2}\phi\right) d\alpha$$

Problem 10 Question d.

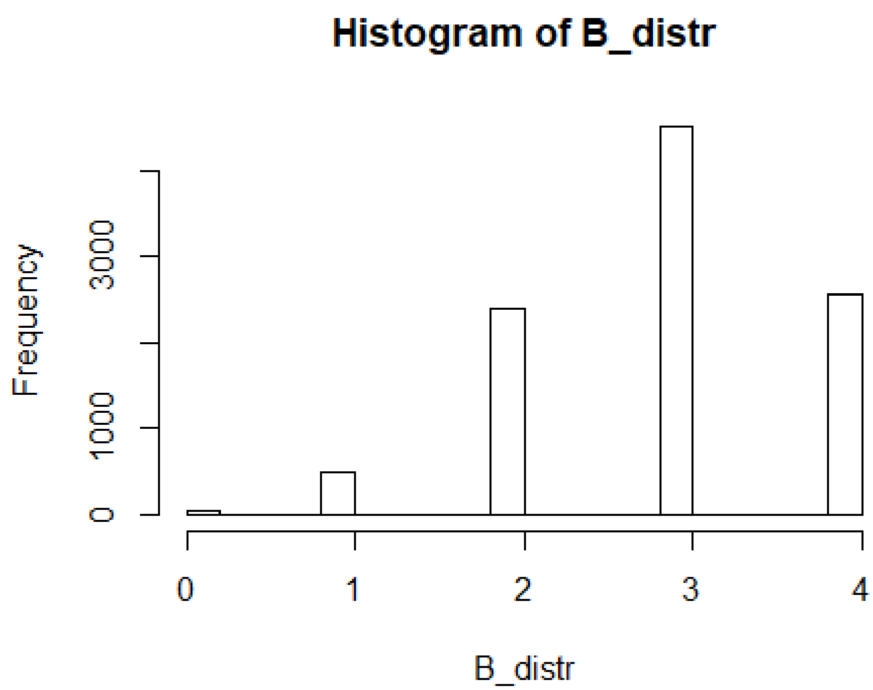
Problem 11

Question a

```
assign_Trt = function(pA = 0.2, pB = 0.8) {
  Treatment = rep(NA,4)
  Treatment[1] = rbinom(1,1,0.5) # 0 for A, 1 for B
  for (i in 2:4) {
    if(Treatment[i-1]==0)
      rep = rbinom(1,1,pA)
    else
      rep = rbinom(1,1,pB)
    if(rep==1)
      Treatment[i] = Treatment[i-1]
    else
      Treatment[i] = 1-Treatment[i-1]
  }
  return(Treatment)
}

N = 10000
B_distr = rep(NA,N)
for (i in 1:N) {
  B_distr[i] = sum(assign_Trt())
```

```
}
hist(B_distr)
```



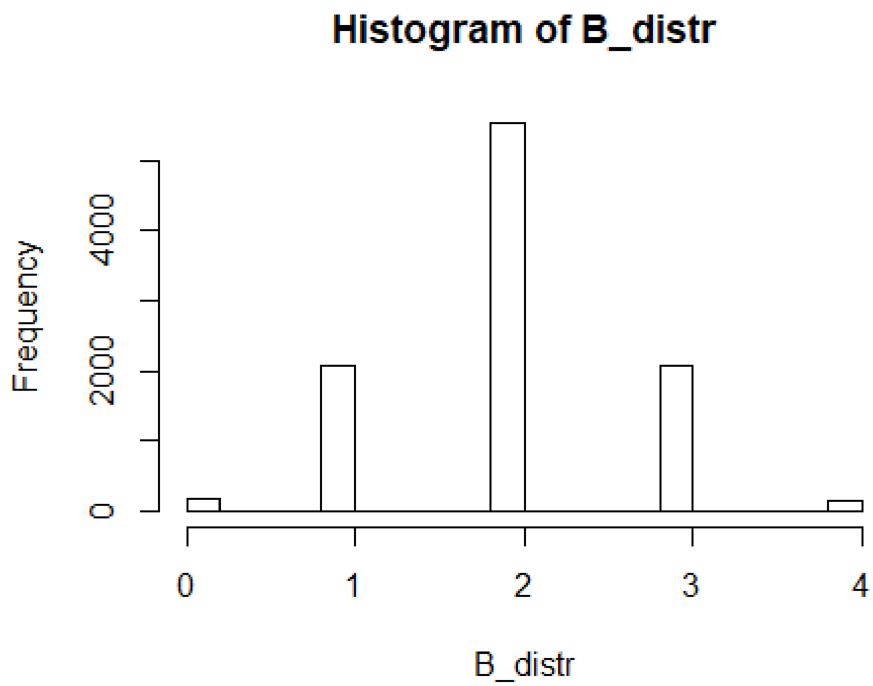

```
data.frame(Times = c(0,1,2,3,4), Freq = c(length(B_distr[B_distr==0])/N,
length(B_distr[B_distr==1])/N, length(B_distr[B_distr==2])/N,
length(B_distr[B_distr==3])/N, length(B_distr[B_distr==4])/N))

##   Times   Freq
## 1     0 0.0037
## 2     1 0.0486
## 3     2 0.2404
## 4     3 0.4513
## 5     4 0.2560
```

Compared to a balanced design, the probability of more patients being assigned to treatment B is higher.

Question b

```
N = 10000
B_distr = rep(NA,N)
for (i in 1:N) {
  B_distr[i] = sum(assign_Trt(pA=0.3, pB=0.3))
}
hist(B_distr)
```




```
data.frame(Times = c(0,1,2,3,4), Freq = c(length(B_distr[B_distr==0])/N,
length(B_distr[B_distr==1])/N, length(B_distr[B_distr==2])/N,
length(B_distr[B_distr==3])/N, length(B_distr[B_distr==4])/N))
```

```
##   Times   Freq
## 1     0 0.0161
## 2     1 0.2064
## 3     2 0.5543
## 4     3 0.2089
## 5     4 0.0143
```

Compared to a balanced design, the probabilities of 0, 1, 3 or 4 patients being assigned to treatment B are higher.

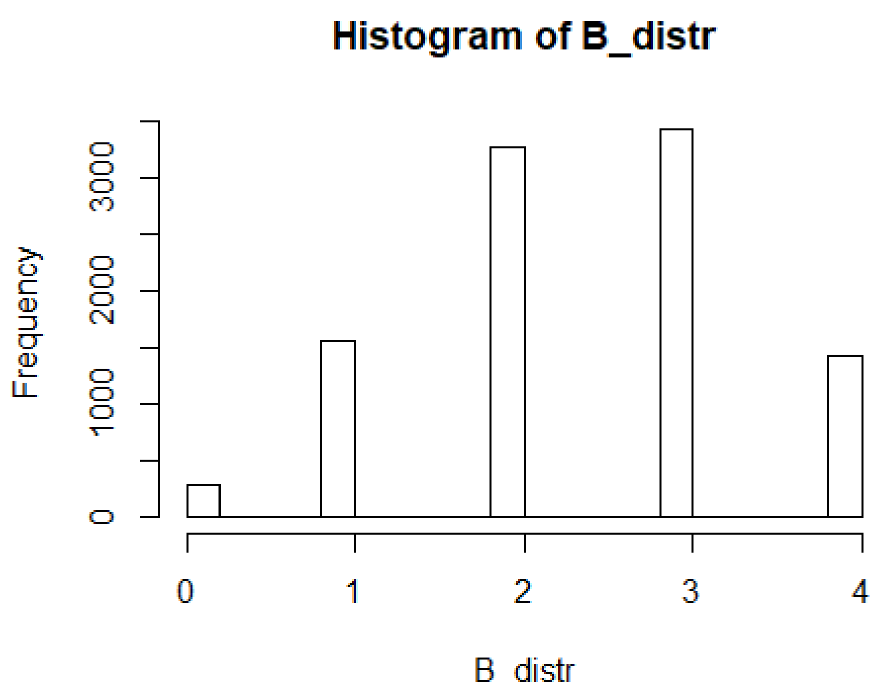
Problem 12

Question a

```
assign_Trt2 = function(pA = 0.2, pB = 0.8) {
  Treatment = rep(NA,4)
  nA = 1 # numbers of A ball
  nB = 1
  for (i in 1:4) {
    Treatment[i] = rbinom(1,1,nB/(nA+nB)) # 0 for A, 1 for B
    if(Treatment[i]==0){
      rep = rbinom(1,1,pA)
      if(rep==1)
```

```r
        nA = nA+1
      else
        nB = nB+1
    }
    else{
      rep = rbinom(1,1,pB)
      if(rep==1)
        nB = nB+1
      else
        nA = nA+1
    }
  }
  return(Treatment)
}

N = 10000
B_distr = rep(NA,N)
for (i in 1:N) {
  B_distr[i] = sum(assign_Trt2())
}
hist(B_distr)
```



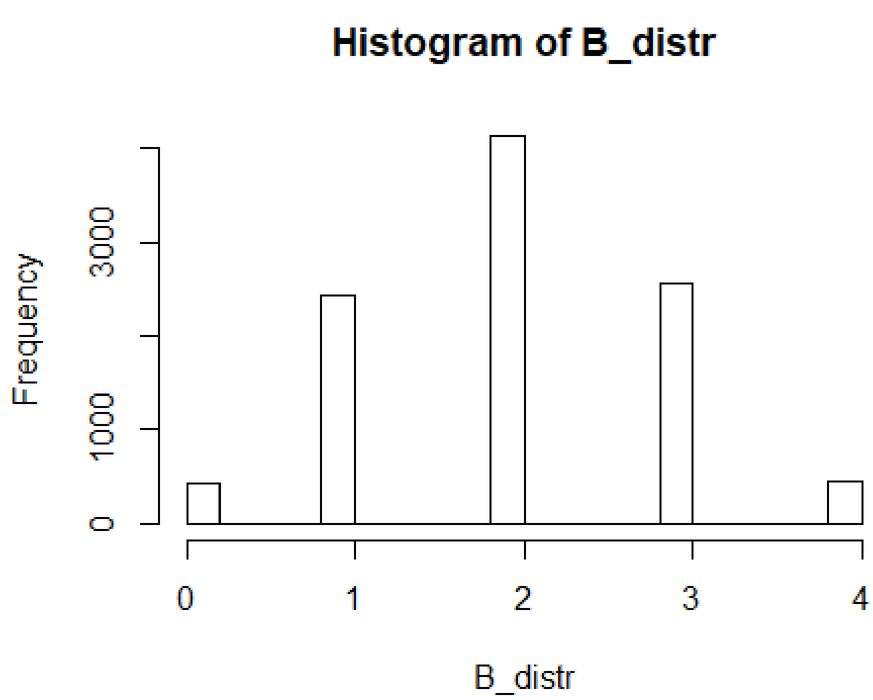

```r
data.frame(Times = c(0,1,2,3,4), Freq = c(length(B_distr[B_distr==0])/N,
length(B_distr[B_distr==1])/N, length(B_distr[B_distr==2])/N,
length(B_distr[B_distr==3])/N, length(B_distr[B_distr==4])/N))
```

```
##   Times   Freq
## 1     0 0.0290
## 2     1 0.1557
## 3     2 0.3283
## 4     3 0.3438
## 5     4 0.1432
```

Compared to a balanced design, the probability of more patients being assigned to treatment B is higher.

Question b

```
N = 10000
B_distr = rep(NA,N)
for (i in 1:N) {
  B_distr[i] = sum(assign_Trt2(pA=0.3, pB=0.3))
}
hist(B_distr)
```




```
data.frame(Times = c(0,1,2,3,4), Freq = c(length(B_distr[B_distr==0])/N,
length(B_distr[B_distr==1])/N, length(B_distr[B_distr==2])/N,
length(B_distr[B_distr==3])/N, length(B_distr[B_distr==4])/N))

##   Times   Freq
## 1     0 0.0439
## 2     1 0.2428
## 3     2 0.4134
```

```
## 4      3 0.2553
## 5      4 0.0446
```

Compared to a balanced design, the probabilities of 0, 1, 3 or 4 patients being assigned to treatment B are higher.

Problem 13

Question a

The type I error rate of the test is 0.05

Question b

$$w_1X_1 \sim N(\mu t_1 w_1, w_1^2), w_2X_2 \sim N(\mu t_2 w_2, w_2^2)$$

$$\begin{aligned} Cov(w_1X_1, w_2X_2) &= E(w_1X_1 - \mu t_1 w_1)(w_2X_2 - \mu t_2 w_2) \\ &= E(w_1X_1w_2X_2 - w_2X_2\mu t_1 w_1 - w_1X_1\mu t_2 w_2 + \mu t_1 w_1 \mu t_2 w_2) \\ &= 2w_1\mu t_1 w_2 \mu t_2 - 2w_2\mu t_2 w_2 \mu t_1 = 0 \end{aligned}$$

$$corr(w_1X_1, w_2X_2) = 0$$

$$Z = w_1X_1 + w_2X_2 \sim N(\mu t_1 w_1 + \mu t_2 w_2, I)$$

$$Z' = Z - \mu t_1 w_1 + \mu t_2 w_2 \sim N(0,1)$$

$$\begin{aligned} Pr(Z > 1.96|\mu > 0) &= Pr((Z - \mu t_1 w_1 + \mu t_2 w_2) > 1.96|\mu > 0) \\ &= 1 - \Phi(1.96 - \mu t_1 w_1 + \mu t_2 w_2) \end{aligned}$$

Question c

According to the equation of power, we can know that the smaller $\mu t_1 w_1 + \mu t_2 w_2$, the bigger the power. So $w_1 = w_2 = \frac{1}{\sqrt{2}}$