# INTRODUCTION

## Simulation Function:

```
simulation(prior.dlt, true.dlt, NS=F, trtDlt=0.2, delta=0.05, r1=0.5,
r2=0.95, nmax=50, nmin=10, a=1.2, b=1, c=4)
```

**Description**:

Bayesian decision-theoretic design is an algorithm that was used to decide the maximum tolerated dose (MTD) for patients in a two-agent phase I trial. MTD is the highest dose combination at which not more than a prespecified proportion of patients experience dose-limiting toxicities (DLTs). The simulation function will simulate a two-agent phase I trials and apply this algorithm during the simulation to determine the recommended MTD. The function will keep track of the number of times that a specific dose combination that was recommend as MTD during 10000 times of simulations.

**Arguments**:

- *prio.dlt*: a 4 x 4 matrix that stores information of prior dose-limiting toxicities (DLTs)
- *true.dlt*: a 4 x 4 matrix that stores the information of real dose-limiting toxicities (DLTs)
- *NS*: a logical variable denotes what kind of dose escalation approaches we prefer. If NS == TRUE, then apply non-skipping method, otherwise apply dose skipping method.
- *trtDlt*: the target dose-limiting toxicities(DLTs). It takes a default value 0.2.
- *delta*: trtDlt + delta is an upper bound on the acceptable DLT probabilities. It takes a default value 0.05
- *r1*: the prespecified probability for stopping rule S3. It takes a default value 0.5.
- *r2*: the prespecified probability for stopping rule S4. It takes a default value 0.95.
- *nmax*: the trial is stopped when the sample size reaches $N_{max}$. It takes a default value 50
- *nmin*: early stopping is prohibited before the sample size reaches $N_{min}$. It takes a default value 10.
- *a*: a specified positive constant. If the selected dose combinations have a DLT probability that is larger than target DLT, we assigned "a" to their utility function. It takes a default value 1.2.
- *b*: a specified positive constant. If the selected dose combinations have a DLT probability that is smaller than target DLT, we assigned "b" to their utility function. It takes a default value 1.
- *c*: a specified positive that use to calculate the initial $a_{ij}$ and $b_{ij}$ from prior mean. It takes a default value 4.

**Return**:

The function will return an R list that includes a 4 x 4 matrix and a numeric number. The matrix contains the information that denotes the number of times a specific dose combination was recommend as MTD during 10000 simulations. And the numeric number is the average sample size of each simulation.

**Examples:**

- Apply skipping approach and consider scenario A as both prior and true DLT.

```
simInfo <- simulation(prior.dlt=scenarioA, true.dlt=scenarioA,  NS = F)
```

- Apply non-skipping approach and consider scenario A as both prior and true DLT

```
simInfo <- simulation(prior.dlt=scenarioA, true.dlt=scenarioA,  NS = T)
```

## Summary Function:

```
summary(true.dlt, simInfo, tableType = 3, trtDlt = 0.2)
```

**Description:**

Summary function is to interpret the list that is returned by simulation function.

**Arguments:**

- *true.dlt*: a 4 x 4 matrix that stores the information of real dose-limiting toxicities (DLTs)
- *simInfo:* a R list. It is the result returned by simulation function
- *tableType:* denotes two different two different form of tables. If tableType = 3, then the output will be organized as the form of table 3, otherwise it would be organized as table 4.
- *tr*tDlt: the target dose-limiting toxicities(DLTs). It takes a default value 0.2.

## USER MANUAL

Suppose we are using DLT from scenario A as our true DLT and code for $LEF^{NS}$, LEF, $LEF^{-}$, $LEF^{+}$ and $LEF^{*}$ will be given as follow respectively. Note that in the follow cases, scenA, preA.* and lfl.*.* represents the true DLT matrix, prior DLT matrix and the result return by simulation function respectively.

- $LEF^{NS}$

```
lfl.ns.a <- simulation(scenA, scenA, T)
summary(scenA, lfl.ns, 3)
```

- LEF

```
lfl.s <- simulation(scenA, scenA)
summary(scenA, lfl.s, 3)
```

- LEF$^{-}$

```
lfl.ls <- simulation(preA.ls, scenA)
summary(scenA, lfl.ls, 4)
```

- LEF$^{+}$

```
lfl.gt <- simulation(preA.gt, scenA)
summary(scenA, lfl.gt, 4)
```

- LEF$^{*}$

```
lfl.rd <- simulation(preA.rd, scenA)
summary(scenA, lfl.rd, 4)
```

In particular, I would like to take the output of LEF$^{NS}$ as an example to explain how to interpret the result of my program. After executing the LEF$^{NS}$ code, you would see a output like this:

```
> lfl.ns.a <- simulation(scenA, true.dlt, T)
> summary(scenA, lfl.ns.a, 3)
         At target     1-10% of target      >10% of target    None recommended Average sample size
                14                  80                   6                   0                  26
```

"At target" 14 means that during the 10000 simulations, 14% of the dose combinations, which were recommended as MTD, have a DLT that is equal to our target DLT(default = 0.2). In this specific case, it means dose combination (2,3) was recommended 1400 times.

"1-10% of target" 80 means during the 10000 simulations, 80% of the dose combinations, which were recommended as MTD, have a DLT that deviated away from the target within 1-10%.

"> 10% of target" 6 means during the 10000 simulations, 6% of the dose combinations, which were recommended as MTD, have a DLT that is larger or less than our target DLT 10%.

"None recommended" 0 means there is no dose combinations are likely to be overly toxic.

"Average Sample Size" means there are average 26 patients involves in each simulations.

# SIMUALATION SUMMARY

| Scenario | Design | Percentage of recommendation | | | None recommended | Average sample size |
|---|---|---|---|---|---|---|
| | | At target | 1-10 pts of target | < or > 10 Pts of target | | |
| A | LFL $^{NS}$ | 13 | 81 | 6 | 0 | 26 |
| | LFL | 20 | 76 | 4 | 0 | 25 |
| B | LFL $^{NS}$ | 0 | 84 | 16 | 0 | 39 |
| | LFL | 0 | 86 | 14 | 0 | 39 |
| C | LFL $^{NS}$ | 55 | 43 | 0 | 2 | 21 |
| | LFL | 53 | 45 | 0 | 1 | 21 |

**Table 3** Operating characteristics of the proposed designs (denoted LFL $^{NS}$ and LFL). LFL$^{NS}$ does not allow dose skipping while LFL allows dose skipping; in both of the designs, the priors are centered at the true DLT probabilities. The percentage of recommendation may not add up to 100 due to rounding errors.

| Scenario | Design | Percentage of recommendation | | | | None recommended | Average sample size |
|---|---|---|---|---|---|---|---|
| | | At target | 1-5 pts of target | 6-10 pts of target | < or > 10 Pts of target | | |
| A | LFL | 20 | 66 | 10 | 4 | 0 | 25 |
| | LFL - | 9 | 65 | 21 | 4 | 0 | 23 |
| | LFL+ | 5 | 80 | 11 | 5 | 0 | 28 |
| | LFL * | 21 | 57 | 17 | 5 | 0 | 26 |
| B | LFL | 0 | 50 | 36 | 14 | 0 | 39 |
| | LFL - | 0 | 57 | 30 | 13 | 0 | 39 |
| | LFL+ | 0 | 41 | 47 | 12 | 0 | 38 |
| | LFL * | 0 | 42 | 47 | 11 | 0 | 40 |
| C | LFL | 53 | 27 | 18 | 0 | 1 | 21 |
| | LFL - | 38 | 44 | 17 | 0 | 1 | 20 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | LFL+ | 54 | 15 | 28 | 0 | 3 | 22 |
| | LFL * | 48 | 30 | 20 | 0 | 2 | 21 |

**Table 4**. Sensitivity analysis. In LFL, the priors are centered at the true DLT probabilities; in LFL- and LFL+, the prior means underestimate and overestimate the true DLT probabilities by 1-5%; in LFL*, both under- and overestimation of 1-5% occur in the prior means. The percentage of recommendation may not add up to 100 due to rounding errors.

## APPRECIATION

During this project, **Kimberley Kondratieff** inspired me of a nice way to summary and organizes the output of my program.

**Shiou-Shiou Deng** helps me clear out some confusion of the Bayesian algorithm.