

## Adaptive GMCP

The package provide function **adaptGMCP\_PC** to perform adaptive weighted multiple testing by using user input values similar to East interim monitoring feature.

### Installation and Loading

We can install the package from the '.gz' compressed file. This is one time activity. If **gmcp** package exists in the machine the installation might show some warning regarding masking some functions/variables from **gmcp** which we can ignore as of now.

Once the installation is complete successfully we can load the package like a usual R package.

```
{r}
#installation of the package

install.packages("C:/Users/ajoy.mukhopadhyay/CIC/R_Packages/AdaptGMCP_0.1.0.tar.gz"
)

library("AdaptGMCP")
```

### Example 1: Parametric Test with modification of weights in the interim(No Selection)

This example is taken from section 8.2.1 in the chapter 8.

Consider the pairwise comparison of the three treatment arms of the Schizophrenia trial to their common control arm, with the three elementary null hypotheses indexed by  $I_1 = \{1, 2, 3\}$ . We will allow the possibility of early rejection with the level-0.025 group sequential O'Brien-Fleming efficacy boundaries  $\alpha_{J,1} = 0.002583$  and no futility boundary at stage one, and the critical cut-off  $c_J = 0.023996$  at stage two, for all intersection hypotheses  $H_J, J \in \mathcal{P}(I_1)$ . A two-stage design in which a graphical testing procedure with  $\alpha$  propagation is adopted at stage one, it consists of three nodes, representing the three null hypotheses  $H_1, H_2, H_3$  with respective initial type-1 error allocations  $(0.5\alpha_1, 0.3\alpha_1, 0.2\alpha_1)$ . Each node  $H_i$  has two edges emanating from it with edge weights that reflect the amount of type-1 error to be propagated to each of the remaining nodes should  $H_i$  be rejected by a weighted hypothesis test. For example, if  $H_3$  is rejected, then 75% of its initial error allocation  $(0.2\alpha)$  will be passed along to  $H_1$  and the remaining 25% will be passed along to  $H_2$ . The graph is plotted as follow by using **gmcp** package.

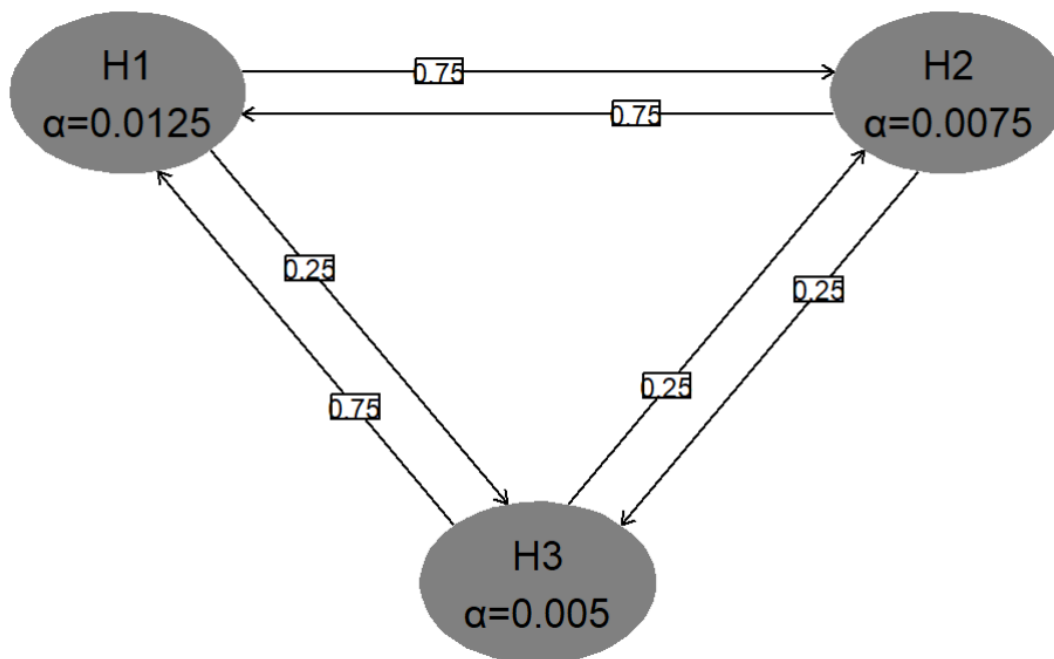
```
{r}

#Initial Weights
WI <- c(0.5,0.3,0.2)

#Transition Matrix
G <- matrix(c(0,0.75,0.25,
              0.75,0,0.25,
              0.75,0.25,0),
            nrow = 3, byrow=T)

#Alpha
alpha <- 0.025

gMCPLite::hGraph(nHypotheses = 3, nameHypotheses = c('H1','H2','H3'),
                 alphaHypotheses = alpha*WI, m = G)
```



The test statistics  $Z_i$  corresponding to the  $i^{th}$  hypothesis  $H_i; i = 1(1)4$  is assumed to be following multivariate Normal distribution with  $corr(Z_i, Z_j) = 0.5$  for all  $i \neq j$

```
{r}

corr <- matrix(c(1,0.5,0.5,
                 0.5,1,0.5,
                 0.5,0.5,1),
               byrow=T, nrow= 3)
```

## Analysis

The trial is with no selection but modification of weights based on the Stage-1 data is allowed. The input of stage-wise raw p-values and the adaptation choice will be performed through **adaptGMCP\_PC** function. Note: **adaptGMCP\_PC** function use combining p-values method to adjust the stage-wise(>1) p-values by using inverse normal function.

$$P_{adj}^{(i)} = 1 - \Phi(w_{i-1} * \Phi^{-1}(1 - p_i) + w_{i-1} * \Phi^{-1}(1 - p_{i-1}) + \dots + w_{i-1} * \Phi^{-1}(1 - p_1))$$

The user needs to provide the weights as vector. The default weights are  $W = \{\sqrt{1/k}, \sqrt{2/k}, \dots, \sqrt{(k-1)/k}\}$  for a k look trial.

For this trial example we will follow the default weights.

```
{r}
adaptGMCP_PC(WI = WI, G = G, Threshold = c(0.002583, 0.023996),
              Correlation = corr, Selection = F, UpdateStrategy = T)
```

### From R Console

Once the above script is executed user will be asked to provide the unadjusted p-values for stage-1 and perform the analysis as follows,

```
User Input for the look : 1
Enter the raw P-Values for H1 : 0.001
Enter the raw P-Values for H2 : 0.002
Enter the raw P-Values for H3 : 0.011
```

```
Analysis results for Look : 1
```

```
Weights for the intersection hypothesis at Look : 1
```

	H1	H2	H3	Weight1	Weight2	Weight3
1	0	0	1	0.000	0.000	1.000
2	0	1	0	0.000	1.000	0.000
3	0	1	1	0.000	0.675	0.325
4	1	0	0	1.000	0.000	0.000
5	1	0	1	0.725	0.000	0.275
6	1	1	0	0.650	0.350	0.000
7	1	1	1	0.500	0.300	0.200

```
Adj P-values for the intersection hypothesis at Look : 1
```

	H1	H2	H3	PAdj1
1	0	0	1	0.011000000
2	0	1	0	0.002000000
3	0	1	1	0.002878899
4	1	0	0	0.001000000
5	1	0	1	0.001351899
6	1	1	0	0.001503236
7	1	1	1	0.001917676

```
Rejection Status of primary Hypothesis at Look : 1
```

H1	H2	H3
TRUE	FALSE	FALSE

It is observed that H1 is rejected under closed testing based on stage-1 data.

For stage-2 testing it has been decided to utilize the weights  $w_2 = 0.75$  and  $w_3 = 0.25$  to test the remaining H2 and H3 hypothesis, this can be done as follows,

```
Change the testing Strategy from the look : 2 (y/n) :
y
Existing Strategy for reference
  H1 H2 H3 weight1 weight2 weight3
1  0  0  1      0  0.000  1.000
2  0  1  0      0  1.000  0.000
3  0  1  1      0  0.675  0.325
Enter the new weights for ( H2, H3 ) as comma seperated values (e.g.- 0.5,0.5) :
0.75,0.25

Enter the elements of the transition matrix G=(gij)
Enter g( H2,H3 ) :
1
Enter g( H3,H2 ) :
1
```

Note: We also need to provide the transition weights for alpha propagation along with the new weights, in this scenario it's 1, i.e. the full allocated alpha will be transferred to remaining hypothesis if the other is rejected.

The final stage analysis will be performed based on the user provided unadjusted p-values(incremental) as per the new strategy as follows,

```
User Input for the look : 2
Enter the raw P-Values for H2 : 0.019
Enter the raw P-Values for H3 : 0.024

Analysis results for Look : 2

Weights for the intersection hypothesis at Look : 2
  H1 H2 H3 weight1 weight2 weight3
1  0  0  1      0  0.000  1.000
2  0  1  0      0  1.000  0.000
3  0  1  1      0  0.675  0.325

Adj P-values for the intersection hypothesis at Look : 2
  H1 H2 H3      PAdj1      PAdj2      Comb_P2
1  0  0  1 0.011000000 0.02400000 0.0012733143
2  0  1  0 0.002000000 0.01900000 0.0002306200
3  0  1  1 0.002878899 0.02391583 0.0004014761
4  1  0  0 0.001000000      NA      NA
5  1  0  1 0.001351899      NA      NA
6  1  1  0 0.001503236      NA      NA
7  1  1  1 0.001917676      NA      NA

Rejection Status of primary Hypothesis at Look : 2
  H1 H2 H3
TRUE TRUE TRUE
```