

gMCP - an R package for a graphical approach to weighted multiple test procedures

Kornelius Rohmeyer

March 20, 2011

Contents

1	Introduction	1
2	Creating the graph	1
2.1	Using R	2
2.1.1	graph2matrix and matrix2graph	3
2.2	Using the GUI	4
3	The sequentially rejective MTP	5
3.1	Using R	5
3.1.1	Adjusted p-values and simultaneous confidence intervals	6
3.2	Using the GUI	7
4	Options and Export	7
4.1	Options	7
4.2	PNG export	7
5	Important TikZ commands for optimizing the reports	7

1 Introduction

This package provides functions and graphical user interfaces for graph based multiple test procedures. These graphs define a weighting strategy for all subsets of null hypotheses and following the closed test procedure weighted tests can be performed on these subsets. In some case shortcuts are available, for example the weighted Bonferroni corrected tests lead to a sequentially rejective multiple test procedure.

At all steps either graphical user interfaces or the R Console, S4 objects and methods can be used. Please note that this is still a beta release and the API will change in future versions.

2 Creating the graph

In the first step a graph that describes the multiple test procedures must be created.

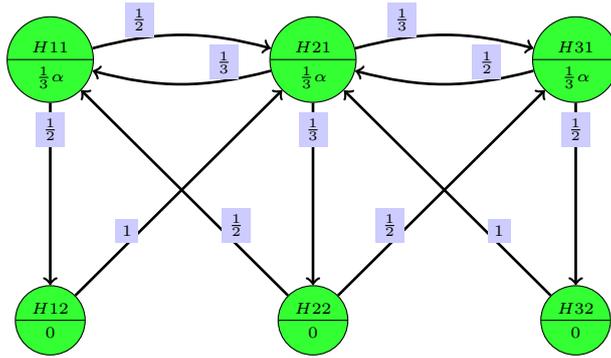


Figure 1: Example graph from [2] that we will create in this vignette.

2.1 Using R

We build upon the package `graph` [4], more precisely we declare a new class `graphMCP` that is a subclass of `graphNEL`. The `initialize` method of this subclass differs only in an extra argument `alpha`, the initial allocation of the significance level `alpha` to the individual hypotheses. Declaration of the nodes and edges is inherited from class `graphNEL`.

As an example we now create the graph from Bretz et al. [2] that you can see in figure 1.

```
> hnodes <- c("H11", "H21", "H31", "H12", "H22", "H32")
> alpha <- c(0.05/3, 0.05/3, 0.05/3, 0, 0, 0)
> edges <- list()
> edges[["H11"]] <- list(edges = c("H21", "H12"), weights = c(1/2, 1/2))
> edges[["H21"]] <- list(edges = c("H11", "H31", "H22"), weights = c(1/3, 1/3, 1/3))
> edges[["H31"]] <- list(edges = c("H21", "H32"), weights = c(1/2, 1/2))
> edges[["H12"]] <- list(edges = "H21", weights = 1)
> edges[["H22"]] <- list(edges = c("H11", "H31"), weights = c(1/2, 1/2))
> edges[["H32"]] <- list(edges = "H21", weights = 1)
> graph <- new("graphMCP", nodes = hnodes, edgeL = edges, alpha = alpha)
```

Let's print the newly created graph:

```
> print(graph)

A graphMCP graph
Overall alpha: 0.05
H11 (not rejected, alpha=0.01667)
H21 (not rejected, alpha=0.01667)
H31 (not rejected, alpha=0.01667)
H12 (not rejected, alpha=0)
H22 (not rejected, alpha=0)
H32 (not rejected, alpha=0)
Edges:
H11 -(0.5)-> H21
H11 -(0.5)-> H12
H21 -(0.3333)-> H11
H21 -(0.3333)-> H31
H21 -(0.3333)-> H22
H31 -(0.5)-> H21
H31 -(0.5)-> H32
H12 -(1)-> H21
H22 -(0.5)-> H11
H22 -(0.5)-> H31
H32 -(1)-> H21
```

Since we also want to visualize the graph, we use the method `nodeRenderInfo` from package `graph` to set appropriate x- and y-coordinates in the `renderInfo`. (We are compatible to the `renderInfo` usage from package `Rgraphviz` [5].)

```
> nodeX <- c(H11 = 100, H21 = 300, H31 = 500, H12 = 100, H22 = 300, H32 = 500)
> nodeY <- c(H11 = 100, H21 = 100, H31 = 100, H12 = 300, H22 = 300, H32 = 300)
> nodeRenderInfo(graph) <- list(nodeX = nodeX, nodeY = nodeY)
```

Coordinates are interpreted as pixels in the GUI and big points in L^AT_EX (72 bp = 1 inch).

Let's take a look at the graph in L^AT_EX rendered with TikZ [7] (you can see the compiled result in figure 1):

```
> cat(graph2latex(graph))

\begin{tikzpicture}[scale=1]
\node (H11) at (100bp,-100bp) [draw,circle split,fill=green!80] {$H11$ \nodepart{lower} $\frac{1}{3}\alpha$};
\node (H21) at (300bp,-100bp) [draw,circle split,fill=green!80] {$H21$ \nodepart{lower} $\frac{1}{3}\alpha$};
\node (H31) at (500bp,-100bp) [draw,circle split,fill=green!80] {$H31$ \nodepart{lower} $\frac{1}{3}\alpha$};
\node (H12) at (100bp,-300bp) [draw,circle split,fill=green!80] {$H12$ \nodepart{lower} $0$};
\node (H22) at (300bp,-300bp) [draw,circle split,fill=green!80] {$H22$ \nodepart{lower} $0$};
\node (H32) at (500bp,-300bp) [draw,circle split,fill=green!80] {$H32$ \nodepart{lower} $0$};
\draw [->,line width=1pt] (H11) to[bend left=15] node[near start,above,fill=blue!20] {$\frac{1}{2}$} (H21);
\draw [->,line width=1pt] (H11) to[auto] node[near start,above,fill=blue!20] {$\frac{1}{2}$} (H12);
\draw [->,line width=1pt] (H21) to[bend left=15] node[near start,above,fill=blue!20] {$\frac{1}{3}$} (H11);
\draw [->,line width=1pt] (H21) to[bend left=15] node[near start,above,fill=blue!20] {$\frac{1}{3}$} (H31);
\draw [->,line width=1pt] (H21) to[auto] node[near start,above,fill=blue!20] {$\frac{1}{3}$} (H22);
\draw [->,line width=1pt] (H31) to[bend left=15] node[near start,above,fill=blue!20] {$\frac{1}{2}$} (H21);
\draw [->,line width=1pt] (H31) to[auto] node[near start,above,fill=blue!20] {$\frac{1}{2}$} (H32);
\draw [->,line width=1pt] (H12) to[auto] node[near start,above,fill=blue!20] {$1$} (H21);
\draw [->,line width=1pt] (H22) to[auto] node[near start,above,fill=blue!20] {$\frac{1}{2}$} (H11);
\draw [->,line width=1pt] (H22) to[auto] node[near start,above,fill=blue!20] {$\frac{1}{2}$} (H31);
\draw [->,line width=1pt] (H32) to[auto] node[near start,above,fill=blue!20] {$1$} (H21);
\end{tikzpicture}
```

We can even change the position of the edge labels for further fine tuning of the graphical representation. With the following command we place the label for the edge from H1 to H2 at position (200, 80):

```
> edgeData(graph, "H11", "H21", "labelX") <- 200
> edgeData(graph, "H11", "H21", "labelY") <- 80
```

2.1.1 graph2matrix and matrix2graph

We can also construct a graph from a given adjacency matrix via the command `matrix2graph`:

```
> m <- matrix(rep(1/3, 16), nrow = 4)
> diag(m) <- c(0, 0, 0, 0)
> graph <- matrix2graph(m)
> print(graph)
```

```
A graphMCP graph
Overall alpha: 0
H1 (not rejected, alpha=0)
H2 (not rejected, alpha=0)
H3 (not rejected, alpha=0)
H4 (not rejected, alpha=0)
Edges:
H1 -(0.3333)-> H2
H1 -(0.3333)-> H3
H1 -(0.3333)-> H4
H2 -(0.3333)-> H1
H2 -(0.3333)-> H3
H2 -(0.3333)-> H4
H3 -(0.3333)-> H1
H3 -(0.3333)-> H2
H3 -(0.3333)-> H4
H4 -(0.3333)-> H1
H4 -(0.3333)-> H2
H4 -(0.3333)-> H3
```

```
> graph2matrix(graph)
```

```
      H1      H2      H3      H4
H1 0.0000 0.3333 0.3333 0.3333
H2 0.3333 0.0000 0.3333 0.3333
H3 0.3333 0.3333 0.0000 0.3333
H4 0.3333 0.3333 0.3333 0.0000
```

2.2 Using the GUI

The creation of `graphMCP` objects is very straight forward, but still takes some time and typos may occur. More convenient for the average user is the use of the graphical user interface for creating and editing MCP graphs that the `gMCP` package includes.

It is called by the command `graphGUI()` and takes as optional argument a variable name, given as a character string, of the graph to edit or under which a newly created `graphMCP` object will be available from the R command line.

```
> graphGUI("graph")
```

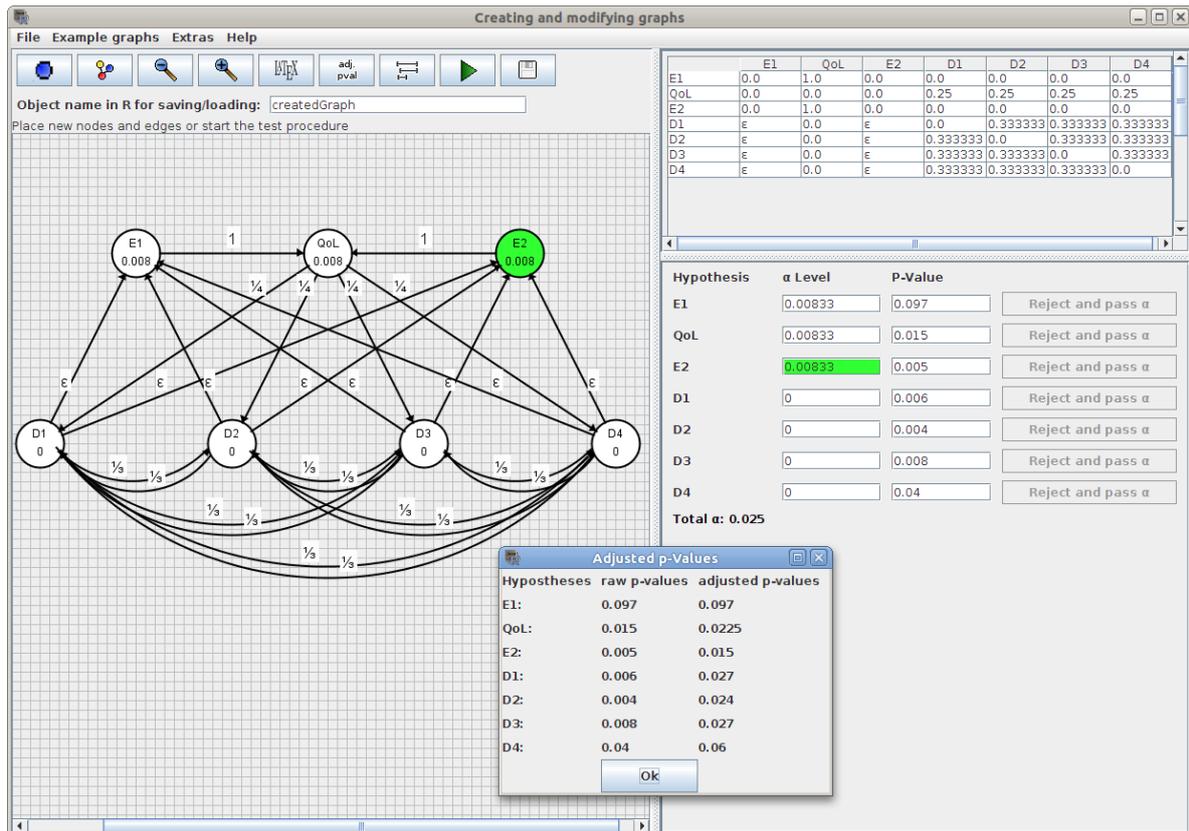


Figure 2: The graphical user interface allows testing, calculation of confidence intervals and adjusted p-values.

Let's take a look at the icon panel:

-  This button lets you add a new node to the graph. After pressing the button click somewhere on the graph panel and a new node will appear at this place.
-  This button lets you add a new edge between two nodes. After pressing the button click on the node the edge should start and after that on the node the edge should end.
-  For really big graphs the ability to zoom in and out is usefull.
-  This button exports the graph as an \LaTeX TikZ picture.
-  Calculates the adjusted p-values.
-  Calculates simultaneous confidence intervals.
-  Starts the testing procedure / goes back to the graph modification.
-  This button exports the graph back to R under the variable name in the adjacent text field.

With drag and drop you can move nodes and also adjust edges.

3 The sequentially rejective MTP

For a full description of the sequentially rejective multiple testing procedure take a look at Bretz et al. [1].

3.1 Using R

You can either specify each rejection step yourself or simply use the method `gMCP`:

```
> graph <- createGraphFromBretzEtAl()
> # We can reject a single node:
> print(rejectNode(graph, "H11"))

A graphMCP graph
Overall alpha: 0.025
H11 (rejected, alpha=0)
H21 (not rejected, alpha=0.0125)
H31 (not rejected, alpha=0.008333)
H12 (not rejected, alpha=0.004167)
H22 (not rejected, alpha=0)
H32 (not rejected, alpha=0)
Edges:
H21 -(0.4)-> H31
H21 -(0.4)-> H22
H21 -(0.2)-> H12
H31 -(0.5)-> H21
H31 -(0.5)-> H32
H12 -(1)-> H21
H22 -(0.5)-> H31
H22 -(0.25)-> H21
H22 -(0.25)-> H12
H32 -(1)-> H21

> # Or given a vector of pvalues let the function gMCP do all the work:
> pvalues <- c(0.1, 0.008, 0.005, 0.15, 0.04, 0.006)
> result <- gMCP(graph, pvalues)
> print(result)

gMCP-Result

P-values:
  H11  H21  H31  H12  H22  H32
0.100 0.008 0.005 0.150 0.040 0.006

Initial graph:
A graphMCP graph
Overall alpha: 0.025
H11 (not rejected, alpha=0.008333)
H21 (not rejected, alpha=0.008333)
H31 (not rejected, alpha=0.008333)
H12 (not rejected, alpha=0)
H22 (not rejected, alpha=0)
H32 (not rejected, alpha=0)
Edges:
H11 -(0.5)-> H21
H11 -(0.5)-> H12
H21 -(0.3333)-> H11
H21 -(0.3333)-> H31
H21 -(0.3333)-> H22
H31 -(0.5)-> H21
H31 -(0.5)-> H32
H12 -(1)-> H21
H22 -(0.5)-> H11
H22 -(0.5)-> H31
H32 -(1)-> H21
```

```

Final graph after 3 steps:
A graphMCP graph
Overall alpha: 0.025
H11 (not rejected, alpha=0.01667)
H21 (rejected, alpha=0)
H31 (rejected, alpha=0)
H12 (not rejected, alpha=0)
H22 (not rejected, alpha=0.008333)
H32 (rejected, alpha=0)
Edges:
H11 -(0.6667)-> H12
H11 -(0.3333)-> H22
H12 -(0.5)-> H11
H12 -(0.5)-> H22
H22 -(1)-> H11

```

>

We can create a TikZ graphic from the last graph with `graph2latex(result@graphs[[4]])` that is shown in figure 3.

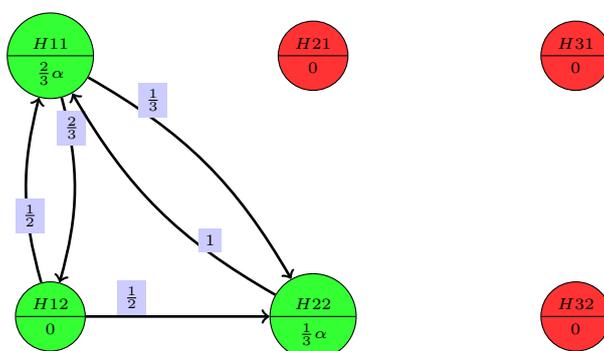


Figure 3: Final graph from the test procedure after rejection of H_{21} , H_{31} and H_{32} .

The command `gMCPReport` generates a full report of the testing procedure:

```
> gMCPReport(result, "Report.tex")
```

3.1.1 Adjusted p-values and simultaneous confidence intervals

Also adjusted p-values and simultaneous confidence intervals can be computed.

Let's assume the tests for hypotheses $H1 : \theta_1 = 0$, $H2 : \theta_2 = 0$ and $H3 : \theta_3 = 0$ are three t-tests with degree of freedom 9. The estimates are $\hat{\theta}_1 = 1.071$, $\hat{\theta}_2 = 0.5575$ and $\hat{\theta}_3 = 1.686$, the sample standard deviations $s_1 = 1.2$, $s_2 = 0.8$ and $s_3 = 1.7$ the t-statistics 2.821, 2.204 and 3.136 and the corresponding p-values $p_1 = 0.02$, $p_2 = 0.055$ and $p_3 = 0.012$. We want to adjust for multiple testing by using the Bonferroni-Holm-Procedure.

```

> # Estimates:
> est <- c("H1"=0.9101444, "H2"=0.4485153, "H3"=1.4568271)
> # Sample standard deviations:
> ssd <- c("H1"=1.2, "H2"=0.8, "H3"=1.7)
> simConfint(createBonferroniHolmGraph(3),
+             pvalues = c(0.02,0.055,0.012),
+             confint = function(node, alpha) {
+                 est[node]+c(-1,1)*qt(1-alpha/2,df=9)*ssd[node]/sqrt(10)
+             })

```

	lower bound	upper bound
H1	-Inf	Inf
H2	-0.1238	1.021
H3	-Inf	Inf

>

3.2 Using the GUI

Use the following two buttons:



See [3].

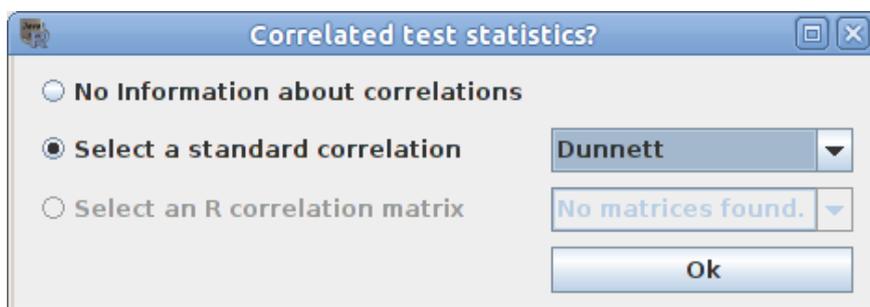


Figure 4: You can also specify a correlation between the tests.

4 Options and Export

4.1 Options

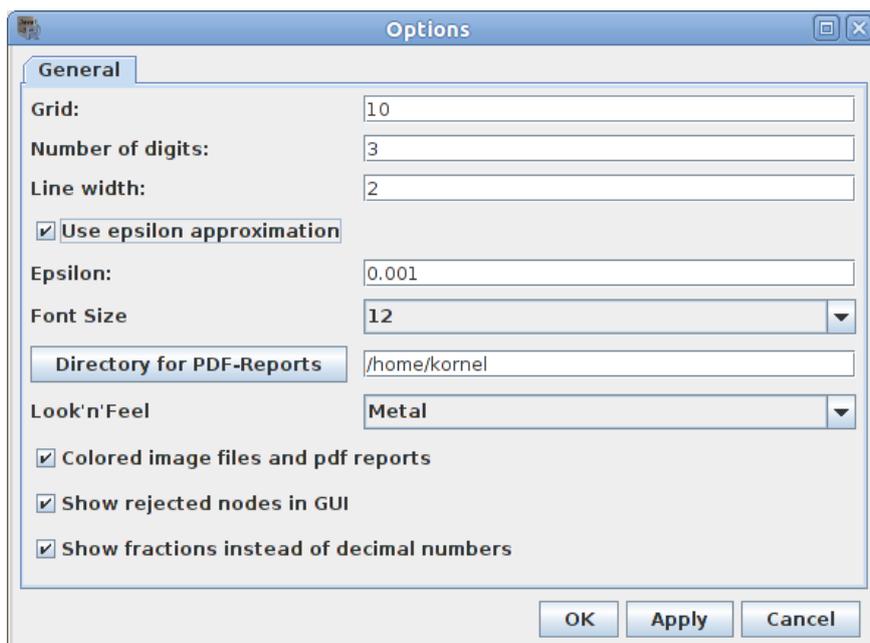


Figure 5: You can configure many things in the option dialog.

4.2 PNG export

5 Important TikZ commands for optimizing the reports

A clear automatic placement of edges and weight labels without overlapping is a very difficult task and for complicated graphs the `gMCP` package will often fail to accomplish this. There is the possibility to adjust the edges and labels in the GUI, but since the \LaTeX graph layout is not (yet) exactly the same, there is perhaps the need for adjusting the graphs in the TikZ code. The TikZ

You can change the position where the edge weight label is placed to `at start`, `very near start`, `near start`, `midway`, `near end`, `very near end` and `at end` or simply use something like `pos=0.5`. If you add an argument `sloped`, the text label will be rotated so that a parallel line to the base line becomes a tangent to the edge.

Often it is useful to reduce the bending angle in `[bend left=15]` below 15. You could also specify and change `out=15` and `in=165` separately.

A powerful feature is the use of styles, since this will effect all objects of a given class. But for this please take a look directly at the TikZ manual [7].

References

- [1] F.~Bretz, W.~Maurer, W.~Brannath, and M.~Posch. A graphical approach to sequentially rejective multiple test procedures. *Statistics in medicine*, 28(4):586–604, 2009. URL www.meduniwien.ac.at/fwf_adaptive/papers/bretz_2009_22.pdf.
- [2] F.~Bretz, W.~Maurer, and G.~Hommel. Test and power considerations for multiple endpoint analyses using sequentially rejective graphical procedures. *Statistics in medicine*, 2010 (in press).
- [3] F.~Bretz, M.~Posch, E.~Glimm, F.~Klinglmueller, W.~Maurer, and K.~Rohmeyer. Graphical approaches for multiple comparison problems using weighted bonferroni, simes or parametric tests. *Biometrical Journal*, page to appear, 2011.
- [4] R.~Gentleman, Elizabeth Whalen, W.~Huber, and S.~Falcon. *graph: A package to handle graph data structures*, 2010. URL <http://CRAN.R-project.org/package=graph>. R package version 1.26.0.
- [5] Jeff Gentry, Li~Long, Robert Gentleman, Seth Falcon, Florian Hahne, Deepayan Sarkar, and Kasper Hansen. *Rgraphviz: Provides plotting capabilities for R graph objects*, 2010. URL <http://www.bioconductor.org/packages/2.6/bioc/html/Rgraphviz.html>. R package version 1.26.0.
- [6] Uwe Kern. *Extending LaTeX's color facilities: the xcolor package*, 2007. URL <http://www.ctan.org/tex-archive/macros/latex/contrib/xcolor/>.
- [7] Till Tantau. *The Tik Z and PGF Packages Manual for version 2.00*, 2008. URL <http://www.ctan.org/tex-archive/graphics/pgf/base/doc/generic/pgf/pgfmanual.pdf>.