The *mgsa* package

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1 Introduction

Model-based Gene Set Analysis (MGSA, Bauer et al. [1]) is a Bayesian modeling approach for gene set enrichment. The package *mgsa* implements MGSA and tools to use MGSA together with the Gene Ontology [2].

2 Quick start

We start with a small simulated dataset which contains `example_go`, a random subset of yeast gene ontology annotations with 20 terms and `example_o`, a simulated set of observed positive genes. These genes could for example be the "hits" of some screen or a set of differentially expressed genes. In the simulation, the terms GO:0006109 and GO:0030663 were active, implying that genes annotated to these terms were more likely to be observed positives than other genes.

```
> library(mgsa)
> data("example")
> example_go
```

```
Object of class MgsaSets
10 sets over 158 unique items.

Set annotations:
                                term             definition
GO:0046292 formaldehyde metabol... The chemical reactio...
GO:0006109 regulation of carboh... Any process that mod...
GO:0008113 peptide-methionine-(... Catalysis of the rea...
GO:0016849 phosphorus-oxygen ly... Catalysis of the cle...
GO:0046527 glucosyltransferase ... Catalysis of the tra...
... and  5  other sets.

Item annotations:
                            name
SFA1    Bifunctional enzyme ...
YJL068C Non-essential intrac...
ADR1    Carbon source-respon...
CAT8    Zinc cluster transcr...
FYV10   Protein of unknown f...
... and  153  other items.
```

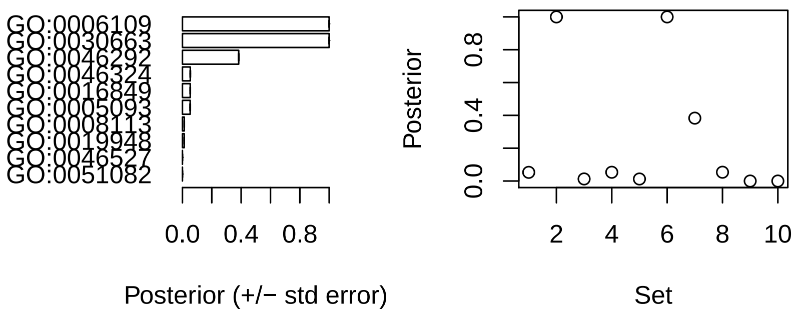
```
> example_o

 [1] "SFA1"    "ADR1"    "CAT8"    "FYV10"   "GCR1"    "GCR2"    "GID7"
 [8] "HAP2"    "HAP3"    "HAP4"    "HAP5"    "PCL10"   "PCL6"    "PCL7"
[15] "PCL8"    "PFK26"   "PFK27"   "PHO85"   "PIG1"    "PIG2"    "REG1"
[22] "SIP4"    "SNF1"    "SNF4"    "TYE7"    "UBC8"    "UBP14"   "VID28"
[29] "YLR345W" "GSC2"    "CCT5"    "CPR6"    "CPR7"    "HSC82"   "PET100"
[36] "TIM9"    "COP1"    "GLO3"    "RET2"    "RET3"    "SEC21"   "SEC26"
[43] "SEC27"
```

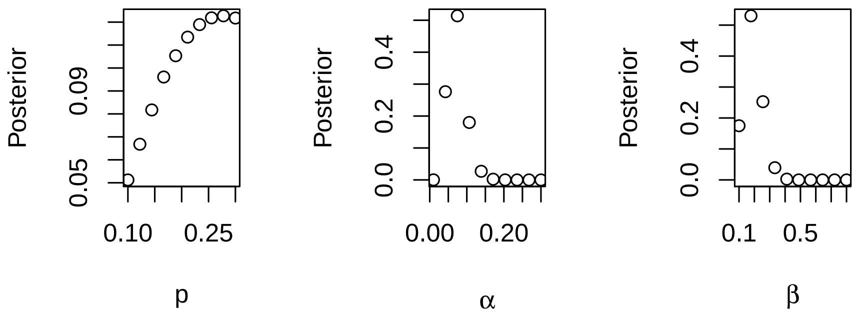
The method mgsa fits the MGSA model. It returns a MgsaMcmcResults object whose print method displays the most likely active terms. On this example, mgsa correctly reports largest posterior probabilities for the terms GO:0006109 and GO:0030663. The call to set.seed(), which sets the seed of the random number generator, simply ensures the example of this vignette to be reproducible. It is not required for mgsa() to work.

```
> set.seed(0)
> fit = mgsa(example_o, example_go)
> fit

Object of class MgsaMcmcResults
158 unique elements in population.
43 unique elements both in study set and in population.
'data.frame':        10 obs. of  4 variables:
 $ inPopulation: int  1 34 2 1 2 8 2 1 21 86
 $ inStudySet  : int  0 28 0 0 0 7 1 0 1 6
 $ estimate    : num  0.053 1 0.0128 0.0534 0.0124 ...
 $ std.error   : num  9.94e-04 5.50e-06 3.19e-04 6.18e-04 2.99e-04 ...
NULL

Posterior on set activity (decreasing order):
           inPopulation inStudySet  estimate    std.error
GO:0006109           34         28 0.9999814 5.500909e-06
GO:0030663            8          7 0.9999640 1.098180e-05
GO:0046292            2          1 0.3831750 1.474526e-03
GO:0046324            1          0 0.0537238 9.021826e-04
GO:0016849            1          0 0.0533820 6.177710e-04
GO:0005093            1          0 0.0529742 9.942573e-04
GO:0008113            2          0 0.0127592 3.187484e-04
GO:0019948            2          0 0.0124324 2.988773e-04
GO:0046527           21          1 0.0000000 0.000000e+00
GO:0051082           86          6 0.0000000 0.000000e+00
```

The method plot provides a graphical visualization of the fit.

```
> plot(fit)
```





3 Using the Gene Ontology

The Gene Ontology [2] (GO) provides structured annotations to genes. Genes with the same annotation consitute a gene set. MGSA can be run on these gene sets. GO annotation files for your organism of study can be downloaded at the GO web page: http://www.geneontology.org.

The function `readGAF` creates an `MgsaGoSets` object, a particular `MgsaSets`, from such a gene annotation file. Note that `readGAF` requires the package `GO.db` and `RSQLite` to be installed.

For illustration purposes, a simplified GO annotation file with only three yeast genes is provided:

```
> readGAF(
+         system.file(
+                 "example_files/gene_association_head.sgd",
+                 package="mgsa"
+         )
+ )

Object of class MgsaGoSets
```

```
113 sets over 3 unique items.

Set annotations:
                              term             definition
GO:0000313     organellar ribosome A ribosome contained...
GO:0000314 organellar small rib... The smaller of the t...
GO:0000315 organellar large rib... The larger of the tw...
GO:0003674      molecular_function Elemental activities...
GO:0003735 structural constitue... The action of a mole...
... and  108  other sets.

Item annotations:
             symbol                    name
S000004660     AAC1 Mitochondrial inner ...
S000007287 15S_RRNA Ribosomal RNA of the...
S000007288 21S_RRNA Mitochondrial 21S rR...
```

4 Using custom gene sets

MGSA is not restricted to Gene Ontology and can be applied to any gene sets. The method `mgsa` can directly be called on such gene sets provided as `list` as in the example below.

```
> mgsa( c("A", "B"), list(set1=LETTERS[1:3], set2=LETTERS[2:5]) )

Object of class MgsaMcmcResults
5 unique elements in population.
2 unique elements both in study set and in population.
'data.frame':        2 obs. of  4 variables:
 $ inPopulation: int  3 4
 $ inStudySet  : int  2 1
 $ estimate    : num  0.5384 0.0923
 $ std.error   : num  0.000909 0.000346
NULL

Posterior on set activity (decreasing order):
     inPopulation inStudySet  estimate    std.error
set1            3          2 0.5383934 0.0009092612
set2            4          1 0.0922680 0.0003464931
```

Internally, the method `mgsa` indexes all elements of the sets before fitting the model. In case `mgsa` must be run on several observations with the same gene sets, computations can be speeded up by performing this indexing once for all. This can be achieved by building a `MgsaSets`.

```
> myset = new( "MgsaSets", sets=list(set1=LETTERS[1:3], set2=LETTERS[2:5]) )
> mgsa(c("A", "B"), myset)

Object of class MgsaMcmcResults
5 unique elements in population.
```

```
2 unique elements both in study set and in population.
'data.frame':        2 obs. of  4 variables:
 $ inPopulation: int  3 4
 $ inStudySet  : int  2 1
 $ estimate    : num  0.537 0.093
 $ std.error   : num  0.000783 0.00029
NULL

Posterior on set activity (decreasing order):
     inPopulation inStudySet  estimate    std.error
set1            3          2 0.5372918 0.0007831928
set2            4          1 0.0929568 0.0002900744
```

```
> mgsa(c("B", "C"), myset)

Object of class MgsaMcmcResults
5 unique elements in population.
2 unique elements both in study set and in population.
'data.frame':        2 obs. of  4 variables:
 $ inPopulation: int  3 4
 $ inStudySet  : int  2 2
 $ estimate    : num  0.456 0.231
 $ std.error   : num  0.0006 0.000572
NULL

Posterior on set activity (decreasing order):
     inPopulation inStudySet  estimate    std.error
set1            3          2 0.4557736 0.0006002762
set2            4          2 0.2305412 0.0005724793
```

References

[1] S. Bauer, J. Gagneur and P. N. Robinson. GOing Bayesian: model-based gene set analysis of genome-scale data. *Nucleic acids research*, 2010.

[2] The Gene Ontology Consortium. Gene Ontology: tool for the unification of biology. *Nature Genetics*, 25:25–29,2000.