Interpretable Gene Set Enrichment Analysis

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Preface

Gene set enrichment analysis is ubiquituous in genetics and genomics research, providing a powerful tool for interpreting the genes that come out of e.g. differential expression analysis. However, the challenge of interpreting a long list of genes is often replaced with the challenge of interpreting a long list of gene sets.

In this work we perform gene set enrichment analysis via sparse multiple regression.

1 GSEA with logistic SuSiE, simulated example

1.1 Loading gene sets from gseasusie

gseasusie::load_gene_sets is a helper function for getting gene sets from different sources in a unified format. It gets curated pathways from the WebGestaltR, MSigDb pathways from msigdbr.

```
#devtools::install_github('karltayeb/gseasusie')
c2 <- gseasusie:::load_msigdb_geneset_x('C2')</pre>
```

loading gene set from msigdbr: C2

We get a flat list where each row is a (gene, gene set) pair.

head(c2\$geneSet)

```
geneSet gene
1 M1423 79026
2 M1423 214
3 M1423 91369
4 M1423 8289
5 M1423 594
6 M1423 146556
```

We also have access to a human readable description of each gene-set

```
head(c2$geneSetDes)
```

```
geneSet gs_cat gs_subcat
    M1423
                         CGP
1
               C2
    M1458
2
               C2
                         CGP
3
    M1481
               C2
                         CGP
   M1439
               C2
4
                         CGP
    M2509
               C2
                         CGP
    M2096
               C2
                         CGP
1
2
3
4
5
```

6 Genes down-regulated in the RCC4 cells (renal cell carcinoma, RCC) expressing VHL [GeneID=

Finally, we have a sparse binary matrix encoding gene set membership.

```
dim(c2$X)
```

Loading required package: Matrix

NULL

1.2 Using logistic SuSiE for gene set enrichment analysis

Point reticulate to a virtual environment with the gibss package installed.

```
library(reticulate)
use_virtualenv('gibss')
```

In this simulation we select 5 random gene sets from the MSigDB C2 ("Curate gene sets") to be enriched. Genes have background log odds of -3 while membership in each gene set increases the log odds by two. The vast majority of genes in this simulation belong to exactly 1 or 0 gene sets.

```
import numpy as np
# a simple simulation
np.random.seed(1)
X = r.c2['X'].toarray().T
```

```
beta0 = -3
beta = np.zeros(X.shape[0])
beta[np.random.choice(beta.size, 5, replace=False)] = 2.
logit = beta @ X + beta0
y = np.random.binomial(1, 1/(1 + np.exp(-logit)))
gibss <- reticulate::import('gibss')</pre>
# get simulation from python session
# just because we want to keep the
X <- py$X
у <- ру$у
tictoc::tic('fitting SER')
serfit <- gibss$susie$fit_logistic_susie2(X, y, L=1, maxiter=1)</pre>
tictoc::toc()
fitting SER: 20.903 sec elapsed
tictoc::tic('fitting SuSiE')
fit <- gibss$susie$fit_logistic_susie2(X, y, L=10, maxiter=10)</pre>
tictoc::toc()
fitting SuSiE: 156.012 sec elapsed
compute_cs <- function(alpha, coverage=0.95){</pre>
  idx <- rev(order(alpha))</pre>
  mass <- cumsum(alpha[idx])</pre>
 last = which(mass >= coverage)[1]
 cs <- idx[1:last]</pre>
  return(list(cs=cs, alpha=alpha[cs], coverage = mass[last], target_coverage=coverage))
}
gseafit <- fit
idx <- which(py$beta !=0)</pre>
alpha <- gseafit$alpha
cs <- purrr::map(1:nrow(alpha), ~compute_cs(alpha[.x,]))</pre>
```

```
[,1]
                      [,2]
                                 [,3]
                                            [,4]
                                                       [,5]
                                                                   [,6]
 [1,] 0.2431641 -0.2924805 -0.2539062 -0.3037109 -0.2539062 -0.5317383
 [2,] 0.3041992 -0.1372070 -0.2856445 -0.2822266 -0.2280273 -0.5375977
 [3,] 0.2812500 -0.2255859 -0.2841797 -0.3261719 -0.2207031 -0.5351562
 [4,] 0.2729492 -0.2070312 -0.2836914 -0.3242188 -0.2172852 -0.5351562
 [5,] 0.2700195 -0.2001953 -0.3090820 -0.3251953 -0.2148438 -0.5336914
 [6,] 0.2685547 -0.1977539 -0.3085938 -0.3242188 -0.2143555 -0.5336914
 [7,] 0.2670898 -0.1958008 -0.3081055 -0.3247070 -0.2133789 -0.5332031
 [8,] 0.2651367 -0.1953125 -0.3090820 -0.3247070 -0.2138672 -0.5336914
 [9,] 0.2641602 -0.1938477 -0.3090820 -0.3247070 -0.2128906 -0.5336914
[10,] 0.2626953 -0.1933594 -0.3095703 -0.3247070 -0.2128906 -0.5341797
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                       [8,]
                                  [,9]
                                            [,10]
                                                        [,11]
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 [3,] -0.2524414 0.09130859 -0.3188477 0.21630859 -0.06591797 -0.4990234
 [4,] -0.2416992 0.11279297 -0.3051758 0.21044922 -0.04882812 -0.5849609
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 [8,] -0.2373047 0.12646484 -0.3041992 0.20458984 -0.21093750 -0.5761719
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                                                              [,18]
          [,13]
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 [3,] -1.549805 -1.937012 -1.203125 -1.318359 -0.7988281 -0.9301758 -0.8842773
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                                                     [,24]
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                     [,21]
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 [5,] 0.4384766 -1.855469 -0.7724609 -1.120605 -0.7353516 -0.22265625
```

```
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 [8,] 0.4038086 -1.855469 -0.7807617 -1.121094 -0.7377930 -0.21630859
 [9,] 0.3930664 -1.854980 -0.7822266 -1.120117 -0.7387695 -0.21533203
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```

```
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```

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                      [,93]
                                 [,94]
                                            [,95]
                                                       [,96]
                                                                     [,97]
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```

```
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 [3,] 0.12890625 -0.7290039 -0.3076172 -0.2744141 0.07128906 -0.8803711
 [4,] 0.25146484 -0.7338867 -0.3041992 -0.2309570 0.23632812 -0.8730469
 [5,] 0.24804688 -0.7338867 -0.3037109 -0.2128906 0.21337891 -0.8691406
```

```
[6,] 0.24462891 -0.7338867 -0.3027344 -0.2119141 0.20703125 -0.8681641
 [7,] 0.24072266 -0.7348633 -0.3017578 -0.2119141 0.20068359 -0.8671875
 [8,] 0.23583984 -0.7363281 -0.3017578 -0.2109375 0.19433594 -0.8671875
 [9,] 0.23291016 -0.7368164 -0.3022461 -0.2104492 0.18847656 -0.8666992
[10,] 0.22851562 -0.7373047 -0.3012695 -0.2104492 0.18261719 -0.8657227
         [,5517]
                    [,5518]
                               [,5519]
                                          [,5520]
                                                     [,5521]
                                                               [,5522]
 [1,] -0.5439453 -0.3154297 -0.4995117 -0.6708984 -0.6518555 0.7656250
 [2,] -0.6201172 -0.2875977 -0.4658203 -0.6577148 -0.8852539 0.6210938
 [3,] -0.6323242 -0.2607422 -0.5151367 -0.6616211 -0.9233398 0.7099609
 [4,] -0.6230469 -0.1953125 -0.5151367 -0.6596680 -0.9399414 0.6928711
 [5,] -0.6215820 -0.1953125 -0.5136719 -0.6586914 -0.9370117 0.6879883
 [6,] -0.6220703 -0.1962891 -0.5131836 -0.6577148 -0.9365234 0.6870117
 [7,] -0.6230469 -0.1967773 -0.5131836 -0.6582031 -0.9360352 0.6860352
 [8,] -0.6245117 -0.1982422 -0.5141602 -0.6586914 -0.9360352 0.6840820
 [9,] -0.6245117 -0.1992188 -0.5141602 -0.6582031 -0.9350586 0.6831055
[10,] -0.6254883 -0.2001953 -0.5141602 -0.6586914 -0.9345703 0.6811523
         [,5523]
                    [,5524]
                               [,5525]
                                          [,5526]
                                                     [,5527]
                                                                [,5528]
 [1,] -0.5244141 -0.4760742 0.1318359 -0.4169922 -0.5151367 -0.5439453
 [2,] -0.4277344 -0.5200195 -0.4843750 -0.6879883 -0.5371094 -0.5903320
 [3,] -0.3989258 -0.4135742 -0.4301758 -0.7050781 -0.5400391 -0.5795898
 [4,] -0.3286133 -0.4208984 -0.5214844 -0.6982422 -0.4746094 -0.5703125
[5,] -0.3320312 -0.4233398 -0.5117188 -0.6967773 -0.4746094 -0.5678711
 [6,] -0.3334961 -0.4233398 -0.5097656 -0.6953125 -0.4741211 -0.5668945
 [7,] -0.3334961 -0.4233398 -0.5083008 -0.6948242 -0.4746094 -0.5659180
 [8,] -0.3349609 -0.4248047 -0.5068359 -0.6948242 -0.4755859 -0.5659180
 [9,] -0.3354492 -0.4252930 -0.5053711 -0.6943359 -0.4760742 -0.5659180
[10,] -0.3359375 -0.4252930 -0.5043945 -0.6938477 -0.4765625 -0.5654297
         [,5529]
                  [,5530]
                              [,5531]
                                         [,5532]
                                                   [,5533] [,5534]
 [1,] -0.5214844 0.8613281 -0.1821289 -0.4169922 0.6147461 2.404785 0.8066406
 [2,] -0.5126953  0.8676758 -0.1840820 -0.2739258  0.4926758  2.142578  1.1298828
 [3,] -0.4951172 0.8198242 -0.1440430 -0.4423828 0.4609375 1.682617 1.2197266
 [4,] -0.4980469 0.8007812 -0.1230469 -0.4282227 0.4492188 1.736816 1.2607422
 [5,] -0.4985352 0.7954102 -0.1162109 -0.4208984 0.4448242 1.755371 1.2749023
 [6,] -0.4990234 0.7949219 -0.1152344 -0.4204102 0.4438477 1.750000 1.2714844
 [7,] -0.4990234 0.7934570 -0.1152344 -0.4199219 0.4433594 1.744141 1.2690430
 [8,] -0.5000000 0.7910156 -0.1157227 -0.4204102 0.4423828 1.737793 1.2651367
[9,] -0.4990234 0.7905273 -0.1152344 -0.4194336 0.4414062 1.731934 1.2617188
[10,] -0.5000000 0.7890625 -0.1152344 -0.4199219 0.4399414 1.725586 1.2587891
         [,5536]
                    [,5537]
                            [,5538]
                                         [,5539]
                                                   [,5540]
                                                               [,5541]
 [1,] -0.4960938 -0.5097656 5.114746 -0.3574219 0.3242188 -0.3457031
 [2,] -0.4707031 -0.5336914 -1.045898 -0.2929688 -0.5800781 -0.4311523
 [3,] -0.4394531 -0.4023438 -1.058105 -0.3627930 -0.5639648 -0.4536133
 [4,] -0.4248047 -0.4116211 -1.019043 -0.3554688 -0.6108398 -0.4599609
```

```
[5,] -0.4184570 -0.3183594 -1.020996 -0.3525391 -0.6079102 -0.4633789
 [6,] -0.4189453 -0.3173828 -1.021484 -0.3520508 -0.6074219 -0.4628906
 [7,] -0.4189453 -0.3173828 -1.021484 -0.3520508 -0.6069336 -0.4638672
 [8,] -0.4199219 -0.3173828 -1.022949 -0.3525391 -0.6074219 -0.4648438
 [9,] -0.4199219 -0.3173828 -1.023438 -0.3515625 -0.6074219 -0.4658203
[10,] -0.4208984 -0.3173828 -1.023926 -0.3520508 -0.6074219 -0.4658203
         [,5542]
                  [,5543] [,5544] [,5545] [,5546]
 [1,] -0.3037109 -0.3325195 -0.5888672 0.3154297 -0.3154297 -0.0390625
 [2,] -0.2460938 -0.2260742 -0.6250000 0.5141602 -0.2949219 -0.3808594
 [3,] -0.2578125 -0.4047852 -0.6328125 0.4843750 -0.2924805 -1.4179688
 [4,] -0.2597656 -0.3945312 -0.6337891 0.4716797 -0.2875977 -1.4409180
 [5,] -0.2617188 -0.3896484 -0.6342773 0.4677734 -0.2866211 -1.4228516
 [6,] -0.2622070 -0.3881836 -0.6342773 0.4663086 -0.2871094 -1.4204102
 [7,] -0.2631836 -0.3876953 -0.6347656 0.4653320 -0.2861328 -1.4179688
 [8,] -0.2646484 -0.3881836 -0.6352539 0.4628906 -0.2875977 -1.4160156
 [9,] -0.2641602 -0.3872070 -0.6357422 0.4614258 -0.2875977 -1.4145508
[10,] -0.2656250 -0.3862305 -0.6347656 0.4599609 -0.2885742 -1.4121094
                   [,5549]
                               [,5550]
                                            [,5551]
                                                       [,5552]
         [,5548]
 [1,] -0.02734375 -0.9980469 -0.21923828 -0.037109375 -0.3422852 -0.4013672
 [2,] -0.04199219 -1.0727539 -0.19677734 0.018066406 -0.3217773 -0.4716797
 [3,] -0.04736328 -1.2490234 -0.07324219 0.007812500 -0.1567383 -0.4887695
[4,] -0.04931641 -1.2275391 -0.08349609 0.007324219 -0.1606445 -0.4326172
 [5,] -0.04882812 -1.2299805 -0.08740234 0.005859375 -0.1635742 -0.4355469
 [6,] -0.04785156 -1.2299805 -0.08740234 0.006347656 -0.1606445 -0.4360352
 [7,] -0.04785156 -1.2309570 -0.08837891 0.005859375 -0.1586914 -0.4365234
 [8,] -0.04882812 -1.2324219 -0.08984375 0.005371094 -0.1582031 -0.4375000
 [9,] -0.04833984 -1.2324219 -0.09033203 0.005371094 -0.1562500 -0.4379883
[10,] -0.04833984 -1.2333984 -0.09179688 0.004882812 -0.1552734 -0.4384766
                  [,5555]
                             [,5556]
                                          [,5557]
                                                       [,5558]
                                                                  [,5559]
       [,5554]
 [1,] 5.805664 -0.5341797 -0.6621094 -0.037109375 -0.002929688 -0.4038086
 [2,] -1.254883 -0.4140625 -0.5654297 0.018066406 -0.022949219 -0.8525391
 [3,] -1.363281 -0.4316406 -0.5380859 0.007812500 0.029785156 -0.8354492
 [4,] -1.398926 -0.4389648 -0.5239258 0.007324219 0.027343750 -0.8247070
 [5,] -1.385254 -0.4414062 -0.5937500 0.007324219 0.027343750 -0.8217773
[6,] -1.382812 -0.4409180 -0.5927734 0.007324219 0.026855469 -0.8208008
 [7,] -1.379395 -0.4404297 -0.5917969 0.007812500 0.026367188 -0.8198242
 [8,] -1.377441 -0.4414062 -0.5908203 0.006835938 0.024414062 -0.8193359
 [9,] -1.374023 -0.4414062 -0.5913086 0.006835938 0.024414062 -0.8193359
[10,] -1.372070 -0.4418945 -0.5913086 0.006347656 0.022460938 -0.8183594
         [,5560]
                   [,5561]
                             [,5562]
                                       [,5563]
                                                  [,5564]
                                                            [,5565]
                                                                      [,5566]
 [1,] -0.1733398 -0.6508789 0.4892578 -0.5600586 12.257812 8.997070 -1.186035
 [2,] -0.7421875 -0.5170898 1.1289062 -0.7866211 -1.368652 -1.154785 -1.227539
 [3,] -0.7783203 -0.3774414 1.5068359 -0.8676758 -1.314453 -1.104980 -1.205566
```

```
[4,] -0.7324219 -0.3906250 1.4443359 -0.8574219 -1.354492 -1.129883 -1.194336
 [5,] -0.7158203 -0.3974609 1.4238281 -0.8544922 -1.345703 -1.119629 -1.198730
 [6,] -0.7133789 -0.4003906 1.4082031 -0.8525391 -1.343262 -1.116211 -1.198730
 [7,] -0.7099609 -0.4033203 1.3940430 -0.8510742 -1.341797 -1.114258 -1.198730
 [8,] -0.7084961 -0.4067383 1.3779297 -0.8496094 -1.340332 -1.112305 -1.199219
 [9,] -0.7065430 -0.4091797 1.3637695 -0.8481445 -1.337891 -1.109863 -1.199219
[10,] -0.7050781 -0.4130859 1.3496094 -0.8466797 -1.336426 -1.107910 -1.199707
         [,5567]
                  [,5568]
                              [,5569]
                                        [,5570]
                                                    [,5571]
                                                               [.5572]
 [1,] -0.9863281 -1.495605 -1.1435547 -0.2358398 -0.2041016 0.02929688
 [2,] -1.1083984 -1.481445 -1.1035156 -0.4111328 -0.1757812 0.11035156
 [3,] -1.0512695 -1.481934 -0.9492188 -0.3339844 -0.1699219 0.12792969
 [4,] -1.0590820 -1.480469 -0.9511719 -0.4086914 -0.1665039 0.13964844
 [5,] -0.9526367 -1.479492 -0.9731445 -0.3354492 -0.1645508 0.14355469
 [6,] -0.9541016 -1.479004 -0.9755859 -0.3374023 -0.1640625 0.14306641
 [7,] -0.9560547 -1.479004 -0.9794922 -0.3393555 -0.1635742 0.14355469
 [8,] -0.9589844 -1.479492 -0.9833984 -0.3417969 -0.1650391 0.14208984
 [9,] -0.9594727 -1.479492 -0.9858398 -0.3432617 -0.1650391 0.14208984
[10,] -0.9619141 -1.480469 -0.9892578 -0.3461914 -0.1655273 0.14160156
                   [,5574]
                             [,5575]
                                        [,5576]
                                                     [,5577]
          [,5573]
                                                                [,5578]
 [1,] -0.04882812 0.8911133 0.8608398 -0.7734375 -0.01708984 -0.5000000
 [2,] -0.05468750 1.0673828 1.4033203 -0.7758789 1.00048828 -0.4960938
 [3,] -0.06054688 1.0146484 1.3364258 -0.7324219 1.03173828 -0.4741211
 [4,] -0.06005859 0.9941406 1.3115234 -0.7363281 0.98876953 -0.4785156
 [5,] -0.06054688 0.9853516 1.3022461 -0.7392578 1.14746094 -0.4794922
 [6,] -0.06005859 0.9794922 1.2978516 -0.7402344 1.13525391 -0.4799805
 [7,] -0.06005859 0.9726562 1.2934570 -0.7407227 1.12255859 -0.4804688
 [8,] -0.06054688 0.9658203 1.2885742 -0.7426758 1.10888672 -0.4814453
 [9,] -0.06054688 0.9594727 1.2846680 -0.7431641 1.09716797 -0.4814453
[10,] -0.06103516 0.9531250 1.2788086 -0.7441406 1.08496094 -0.4824219
         [,5579]
                   [,5580]
                              [,5581]
                                          [,5582]
                                                     [,5583]
                                                                [,5584]
 [1,] -0.1899414 -0.7636719 -0.1118164 0.07519531 -0.3383789 -0.3305664
 [2,] 0.1484375 -0.8183594 1.3735352 0.14111328 -0.3276367 -0.2656250
[3,] 0.2084961 -0.7416992 1.4985352 0.12548828 -0.3354492 -0.4091797
 [4,] 0.1933594 -0.7558594 1.4375000 0.12158203 -0.3344727 -0.4028320
 [5,] 0.1870117 -0.7587891 1.5966797 0.11962891 -0.3339844 -0.4008789
 [6,] 0.1840820 -0.7597656 1.5800781 0.11767578 -0.3339844 -0.3994141
 [7,] 0.1821289 -0.7617188 1.5639648 0.11572266 -0.3339844 -0.3994141
 [8,] 0.1772461 -0.7641602 1.5478516 0.11328125 -0.3344727 -0.3999023
 [9,] 0.1748047 -0.7651367 1.5317383 0.11230469 -0.3344727 -0.3994141
[10,] 0.1708984 -0.7675781 1.5156250 0.10986328 -0.3344727 -0.3994141
                 [,5586] [,5587] [,5588] [,5589]
       [,5585]
                                                           [,5590]
                                                                       [,5591]
 [1,] -1.640137 -0.4702148 -1.065430 -1.318848 2.735840 0.008300781 -0.7104492
 [2,] -1.645508 -0.5136719 -1.143555 -1.437500 2.120117 0.103027344 -0.6308594
```

```
[3,] -1.626953 -0.5249023 -1.307129 -1.440918 2.321777 0.081542969 -0.6064453
 [4,] -1.626465 -0.5268555 -1.311035 -1.438477 2.231934 0.130371094 -0.5937500
 [5,] -1.622070 -0.5268555 -1.310547 -1.438477 2.201660 0.148437500 -0.5898438
 [6,] -1.622070 -0.5273438 -1.309082 -1.437988 2.186523 0.147460938 -0.5898438
 [7,] -1.623047 -0.5268555 -1.309082 -1.437988 2.172363 0.146972656 -0.5898438
 [8,] -1.624512 -0.5278320 -1.309570 -1.437988 2.157715 0.144042969 -0.5903320
 [9,] -1.624023 -0.5273438 -1.308594 -1.438477 2.144043 0.142578125 -0.5903320
[10,] -1.625000 -0.5278320 -1.308594 -1.438477 2.129883 0.141113281 -0.5908203
         [,5592]
                   [,5593]
 [1,] -0.3637695 -1.488770
 [2,] -0.2573242 -2.019043
 [3,] -0.2285156 -1.991699
 [4,] -0.2153320 -2.035645
 [5,] -0.2104492 -2.000000
 [6,] -0.2104492 -1.997070
 [7,] -0.2114258 -1.994629
 [8,] -0.2124023 -1.993164
 [9,] -0.2128906 -1.991211
[10,] -0.2143555 -1.989746
# the CSs fo the first 3 are singletons,
# while the CS for th 4th component has 10 gene sets
```

[1] 1 1 1 10 4783 4786 4788 4790 4792 4793

purrr::map_int(cs, ~length(.x\$cs))

```
# the PIP of the top SNP in each CS
purrr::map_dbl(cs, ~.x$alpha[1])
```

```
[1] 1.000000000 1.000000000 0.999664366 0.767335176 0.012049827 0.010503333 [7] 0.009337636 0.008434772 0.007704303 0.007101273
```

```
# check if the top snp is causal
purrr::map_int(cs, ~.x$cs[1]) %in% idx
```

[1] TRUE TRUE TRUE TRUE FALSE FALSE FALSE FALSE FALSE

We can see that each of the singleton CSs identify on of the "active" gene sets. The 4th CS captures one of the two remaining effects. The SNP with the top PIP is the causal SNP. The CSs corresponding to the other effects (L5-L10) are very large, containing thousands of GSs,

and the maximum PIP is small (< 0.1). We also see the the log BF for the SER, which quantifies the evidence for any one SNP having an effect over the global null favor the null hypothesis.

```
# check which CSs include which of the causal variables
incidence <- do.call(rbind, purrr::map(1:10, ~as.integer(idx %in% cs[[.x]]$cs)))
rownames(incidence) <- paste0('L', 1:nrow(incidence))
colnames(incidence) <- paste0('GS', 1:ncol(incidence))
incidence</pre>
```

	GS1	GS2	GS3	GS4	GS5
L1	0	0	0	0	1
L2	1	0	0	0	0
L3	0	1	0	0	0
L4	0	0	0	1	0
L5	0	0	1	1	0
L6	0	0	1	1	0
L7	0	0	1	1	0
L8	0	0	1	1	0
L9	0	0	1	1	0
L10	0	0	1	1	0

We compare the results against a marginal (on GS at a time) analysis, which is typical for GSEA. The most direct comparison would be to the Baysian logistic regression with fixed prior variance.

The GS discovered in L1-3 correspond to the three strongest marginal effects. However, we see that the GS captures in L4 has the 16th strongest marginal effect. We see that the causal GS that is not discovered in our analysis has the 144th strongest association, and a log BF of ≈ 2.77 , corresponding to a BF of ≈ 16 . Jeffreys proposed a threshold of 10 for "strong" evidence, while Kass and Raftery later propose a treshold of 20, so we will call this "moderately-strong" evidence of association. However, due to the multiple testing burden we judge it approporiate that this effect was not reported.

```
library(dplyr)
```

```
Attaching package: 'dplyr'

The following objects are masked from 'package:stats':

filter, lag
```

The following objects are masked from 'package:base':

intersect, setdiff, setequal, union

```
marginal_analysis <- tibble::tibble(
   GS = colnames(c2$X),
   i = 1:ncol(c2$X),
   lbf=serfit$lbf[1,],
   effect=serfit$effect[1,]
)

marginal_analysis %>%
   mutate(causal = i %in% idx) %>%
   arrange(desc(lbf)) %>%
   mutate(rank = 1:n()) %>%
   filter(causal)
```

```
# A tibble: 5 x 6
         i lbf effect causal rank
 <chr> <int> <dbl> <dbl> <lgl> <int>
1 M8520 4347 146.
                    2.14 TRUE
                                   1
                                   2
2 M2526
       458 35.5
                   1.87 TRUE
3 M847
        487 20.9
                    2.24 TRUE
                                  3
4 M1092 3179 11.2 2.51 TRUE
                                  16
5 M4085 1661 2.77 1.26 TRUE
                                 144
```

Which causal gene sets are driving the association of the 4-15th top marginal gene sets? They all have substantial overlap with M8520, the top marginal enrichment.

```
middle_gene_sets <- marginal_analysis %>%
  mutate(causal = i %in% idx) %>%
  arrange(desc(lbf)) %>%
  mutate(ran = 1:n()) %>%
  head(15) %>% tail(12) %>%
  {.$i}
Matrix::t(c2$X[,middle_gene_sets]) %*% (c2$X[, idx])
```

```
12 x 5 sparse Matrix of class "dgCMatrix" M2526 M847 M4085 M1092 M8520 M16010 3 2 1 . 121
```

```
M2066
                   2
                                       30
M15664
                   1
                                       97
                   4
M18506
                                       58
                          1
M1037
                   1
                                       43
M34027
                          1
                                       75
M2368
                   7
                          1
             5
                                      154
M5198
                   1
                                       56
M3766
                   1
                                       93
                   2
M2608
                                       65
M7357
             1
                   1
                          2
                                       50
M10739
                   2
                                       45
```

In this simulation, although the causal gene set are for genes upregulated in non-small cell lung cancers, we see that there are gene sets associated with immune response, cell cycle, and a host of other cancers. The data show overwhelming support for the top effect. Conditional on the first effect, the other gene sets are no longer predictive of inclusion in the list of genes provided. However, the extremely strong marginal enrichments in these other gene sets and cancer types would obscure this result.

```
marginal_analysis %>%
  arrange(desc(lbf)) %>%
  head(15) %>%
  rename(geneSet = GS) %>%
  left_join(select(c2$geneSetDes, c(geneSet, description))) %>%
  select(c(geneSet, description, lbf))
```

Joining with `by = join_by(geneSet)`

```
# A tibble: 15 x 3
  geneSet description
                                                                              1bf
   <chr>
           <chr>
                                                                             <dbl>
1 M8520
           Cluster 6 of method A: up-regulation of these genes in patient~ 146.
2 M2526
           Genes representing a co-expression network in atopic CD4 [Gene~
                                                                             35.5
           Genes up-regulated in group C of tumors arising from overexpre~
3 M847
                                                                             20.9
4 M16010
           Genes down-regulated in H1975 cells (non-small cell lung cance~
                                                                             19.0
5 M2066
           A list of known cell cycle regulated genes that was compiled f~
                                                                             18.3
6 M15664
           The 'Cervical Cancer Proliferation Cluster' (CCPC): genes whos~
                                                                             17.4
7 M18506
           Genes down-regulated in the ANBL-6 cell line (multiple myeloma~
                                                                             16.2
8 M1037
           Genes up-regulated in gastric cancer cell lines: doxorubicin [~
                                                                             15.1
9 M34027
           Genes down-regulated on infection of normal human bronchial ep~
                                                                             14.7
10 M2368
           Genes up-regulated during later stage of differentiation of Ol~
                                                                             12.7
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11 M5198	Genes down-regulated in quiescent vs dividing CD34+ [GeneID=88~	12.6
12 M3766	Up-regulated genes whose expression correlated with histologic~	12.5
13 M2608	Cell cycle genes significantly (p =< 0.05) changed in fibrobla~	12.3
14 M7357	Genes up-regulated at early stages of progenitor T lymphocyte ~	12.0
15 M10739	Genes down-regulated in ANBL-6 cell line (multiple myeloma, MM~	11.4

2 Summary

In summary, this book has no content whatsoever.

1 + 1