Fused Sparse Structural Equation Models to Jointly Infer Gene Regulatory Network (fssemR)

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In this vignette, we introduce the functionality of the `fssemR` package to estimate the differential gene regulatory network by gene expression and genetic perturbation data. To meet the space and time constraints in building this vignette within the `fssemR` package, we are going to simulate gene expression and genetic perturbation data instead of using a real dataset. For this purpose, we will use function `randomFSSEMdata` in `fssemR` to generate simulated data, and then apply fused sparse structural equation model (FSSEM) to estimate the GRNs under two different conditions and their differential GRN. Also, please go to `https://github.com/Ivis4ml/fssemR/tree/master/inst` for more large dataset analysis. In conlcusion, this vignette is composed by three sections as follow,

- Simulating two GRNs and their eQTL effects under two different conditions
- Estimating GRNs from the simulated gene expression data and genetic perturbation data
- Differential GRN Visualization

For user using package `fssemR`, please cite the following article:

Xin Zhou and Xiaodong Cai. Inference of Differential Gene Regulatory Networks Based on Gene Expression and Genetic Perturbation Data. Bioinformatics, submitted.

Simulating two GRNs and their eQTL effects under two different conditions (Acyclic example)

We are going to simulate two GRNs and their corresponding gene expression and genetic perturbation data in the following steps:

1. Load the necessary packages

```
library(fssemR)
library(network)
> network: Classes for Relational Data
> Version 1.13.0.1 created on 2015-08-31.
> copyright (c) 2005, Carter T. Butts, University of California-Irvine
>                     Mark S. Handcock, University of California -- Los Angeles
>                     David R. Hunter, Penn State University
>                     Martina Morris, University of Washington
>                     Skye Bender-deMoll, University of Washington
>  For citation information, type citation("network").
>  Type help("network-package") to get started.
library(ggnetwork)
> Loading required package: ggplot2
library(Matrix)
```

2. Simulate 20 genes expression data from a directed acyclic networks (DAGs) under two conditions, and each gene is simulated having average 3 cis-eQTLs. Also, the genotypes of corresponding eQTLs are generated from F2-cross.

```
n = c(100, 100)     # number of observations in two conditions
p = 20              # number of genes in our simulation
```

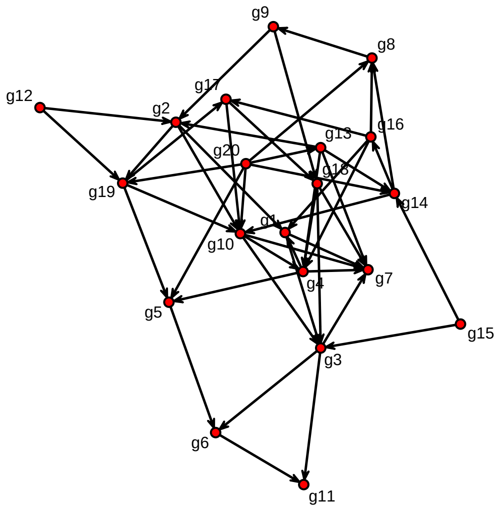

Figure 1: Simulated GRN under condition 1

```
k = 3                # each gene has nonzero 3 cis-eQTL effect
sigma2 = 0.01        # simulated noise variance
prob = 4             # average number of edges connected to each gene
type = "DG"          # `fssemR` also offers simulated ER and directed graph (DG) network
dag  = TRUE          # if DG is simulated, user can select to simulate DAG or DCG
seed = as.numeric(Sys.time())  # any seed acceptable
## seed = 100          # set.seed(100)
set.seed(seed)
data = randomFSSEMdata2(n = n, p = p, k = p * k, sparse = prob / 2, df = 0.3,
                        sigma2 = sigma2, type = type, dag = T)
```

- Summary of simulated GRNs under two conditions, for simplicity, we named our simulated genes as `g{%d}` and eQTLs as `rs{%d}`.

```
# data$Vars$B[[1]]    ## simulated GRN under condition 1
GRN_1 = network(t(data$Vars$B[[1]]) != 0, matrix.type = "adjacency", directed = TRUE)
> <sparse>[ <logic> ] : .M.sub.i.logical() maybe inefficient
plot(GRN_1, displaylabels = TRUE, label = network.vertex.names(GRN_1), label.cex = 0.5)
```

```
# data$Vars$B[[2]]    ## simulated GRN under condition 2
GRN_2 = network(t(data$Vars$B[[2]]) != 0, matrix.type = "adjacency", directed = TRUE)
> <sparse>[ <logic> ] : .M.sub.i.logical() maybe inefficient
plot(GRN_2, displaylabels = TRUE, label = network.vertex.names(GRN_2), label.cex = 0.5)
```

```
# data$Vars$B[[2]]    ## simulated GRN under condition 2
diffGRN = network(t(data$Vars$B[[2]] - data$Vars$B[[1]]) != 0, matrix.type = "adjacency", directed = TRU
> <sparse>[ <logic> ] : .M.sub.i.logical() maybe inefficient
ecol = 3 - sign(t(data$Vars$B[[2]] - data$Vars$B[[1]]))
plot(diffGRN, displaylabels = TRUE, label = network.vertex.names(GRN_2), label.cex = 0.5, edge.col = ec
```

- Simulated eQTLs's effect for 20 genes.

```
library(Matrix)
print(Matrix(data$Vars$F, sparse = TRUE))
> 20 x 60 sparse Matrix of class "dgCMatrix"
>    [[ suppressing 60 column names 'rs1', 'rs2', 'rs3' ... ]]
```

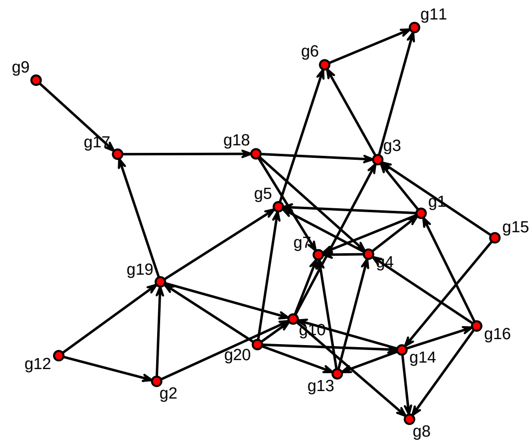

Figure 2: Simulated GRN under condition 2

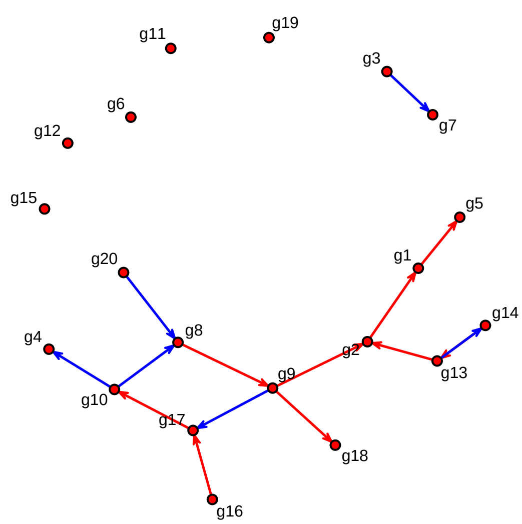

Figure 3: Simulated differential GRN (GRN2 - GRN1), up-regulated are red and down-regulated are blue

```
>
> g1  1 . . . . . . . . . . . . . . . . . . . 1 . . . . . . . . . . . . . .
> g2  . 1 . . . . . . . . . . . . . . . . . . . 1 . . . . . . . . . . . . .
> g3  . . 1 . . . . . . . . . . . . . . . . . . . 1 . . . . . . . . . . . .
> g4  . . . 1 . . . . . . . . . . . . . . . . . . . 1 . . . . . . . . . . .
> g5  . . . . 1 . . . . . . . . . . . . . . . . . . . 1 . . . . . . . . . .
> g6  . . . . . 1 . . . . . . . . . . . . . . . . . . . 1 . . . . . . . . .
> g7  . . . . . . 1 . . . . . . . . . . . . . . . . . . . 1 . . . . . . . .
> g8  . . . . . . . 1 . . . . . . . . . . . . . . . . . . . 1 . . . . . . .
> g9  . . . . . . . . 1 . . . . . . . . . . . . . . . . . . . 1 . . . . . .
> g10 . . . . . . . . . 1 . . . . . . . . . . . . . . . . . . . 1 . . . . .
> g11 . . . . . . . . . . 1 . . . . . . . . . . . . . . . . . . . 1 . . . .
> g12 . . . . . . . . . . . 1 . . . . . . . . . . . . . . . . . . . 1 . . .
> g13 . . . . . . . . . . . . 1 . . . . . . . . . . . . . . . . . . . 1 . .
> g14 . . . . . . . . . . . . . 1 . . . . . . . . . . . . . . . . . . . 1 .
> g15 . . . . . . . . . . . . . . 1 . . . . . . . . . . . . . . . . . . . 1
> g16 . . . . . . . . . . . . . . . 1 . . . . . . . . . . . . . . . . . . .
> g17 . . . . . . . . . . . . . . . . 1 . . . . . . . . . . . . . . . . . .
> g18 . . . . . . . . . . . . . . . . . 1 . . . . . . . . . . . . . . . . .
> g19 . . . . . . . . . . . . . . . . . . 1 . . . . . . . . . . . . . . . .
> g20 . . . . . . . . . . . . . . . . . . . 1 . . . . . . . . . . . . . . .
>
> g1  . . . . . 1 . . . . . . . . . . . . . . . . . . .
> g2  . . . . . . 1 . . . . . . . . . . . . . . . . . .
> g3  . . . . . . . 1 . . . . . . . . . . . . . . . . .
> g4  . . . . . . . . 1 . . . . . . . . . . . . . . . .
> g5  . . . . . . . . . 1 . . . . . . . . . . . . . . .
> g6  . . . . . . . . . . 1 . . . . . . . . . . . . . .
> g7  . . . . . . . . . . . 1 . . . . . . . . . . . . .
> g8  . . . . . . . . . . . . 1 . . . . . . . . . . . .
> g9  . . . . . . . . . . . . . 1 . . . . . . . . . . .
> g10 . . . . . . . . . . . . . . 1 . . . . . . . . . .
> g11 . . . . . . . . . . . . . . . 1 . . . . . . . . .
> g12 . . . . . . . . . . . . . . . . 1 . . . . . . . .
> g13 . . . . . . . . . . . . . . . . . 1 . . . . . . .
> g14 . . . . . . . . . . . . . . . . . . 1 . . . . . .
> g15 . . . . . . . . . . . . . . . . . . . 1 . . . . .
> g16 1 . . . . . . . . . . . . . . . . . . . 1 . . . .
> g17 . 1 . . . . . . . . . . . . . . . . . . . 1 . . .
> g18 . . 1 . . . . . . . . . . . . . . . . . . . 1 . .
> g19 . . . 1 . . . . . . . . . . . . . . . . . . . 1 .
> g20 . . . . 1 . . . . . . . . . . . . . . . . . . . 1
```

Therefore, the B matrices and F matrix in `data$Vars` are the true values in our simulated model. We then need to estimated the $\hat{B}$ and $\hat{F}$ by the FSSEM algorithm.

Estimating GRNs from the simulated gene expression data and genetic perturbation data

We need to input the gene expression and corresponding genotype data of two conditions into the FSSEM algorithm. They are stored in the `data$Data`.

1. 20 simulated gene expression under two conditions

```
head(data$Data$Y[[1]])
>         [,1]      [,2]      [,3]      [,4]      [,5]      [,6]      [,7]
> g1  6.463465  5.001151  4.709183  6.980125  7.131554  4.602149  6.614780
> g2 -5.397134 -6.700854 -6.700718 -4.985990 -7.339566 -6.732214 -6.577636
> g3 10.921035 12.167808  9.656205  9.663098 11.775005 11.760271 12.414851
> g4  1.408550  4.787821  5.847085  1.104141  5.517687  4.660480  4.890725
> g5  9.909330 11.682665 13.889057 11.908029 13.598678 14.650058 12.021129
> g6  5.199521  4.419677  4.929860  7.275309  7.352447  5.711886  4.469941
>         [,8]      [,9]     [,10]     [,11]     [,12]     [,13]     [,14]
> g1  5.118519  6.336698  4.899318  7.861687  5.186484  3.763718  5.112579
> g2 -7.313459 -4.636815 -2.059818 -3.722527 -4.507236 -6.131678 -5.381144
> g3  9.867780 12.521853 12.855199 13.316023 13.679524 11.208787 12.853941
> g4  4.011654  5.421340  6.923733  2.088182  2.117062  5.395962  5.653794
> g5 13.314392 14.189589 15.310641 12.241274 12.168393 13.053649 13.457780
> g6  6.572868  6.337745  4.554980  3.515648  5.141726  6.255022  6.929912
>        [,15]     [,16]     [,17]     [,18]     [,19]     [,20]     [,21]
> g1  5.903988  6.724546  6.443118  5.451373  4.992221  3.055172  3.804466
> g2 -6.520312 -6.689233 -4.326681 -4.912865 -5.409182 -4.885673 -7.747699
> g3 12.999579 12.380117 12.376087 12.784060 13.763989 14.748521 13.196278
> g4  3.306147  4.813625  3.898871  1.840185  4.464428  1.747595  3.755452
> g5 12.692054 11.972664 13.170665 11.321381 11.814652 12.518966 14.961964
> g6  4.397486  6.410016  4.797401  4.996343  5.217998  6.047510  8.397211
>        [,22]     [,23]     [,24]     [,25]     [,26]     [,27]     [,28]
> g1  4.888591  7.974643  4.178480  6.579236  3.865100  3.243895  7.373110
> g2 -3.611766 -5.129023 -5.026690 -6.306042 -4.680695 -2.370635 -8.894388
> g3  9.990711 12.203795 12.016466 12.583286 14.373721 16.805902 12.137856
> g4  5.157593  2.208016  3.912920  4.426840  4.797241  5.263364  4.754790
> g5 14.118605 13.941945 14.466893 11.067572 13.802861 14.917070 11.717492
> g6  7.816908  5.381761  4.415643  4.154777  8.576528  6.283995  5.525972
>        [,29]     [,30]     [,31]     [,32]     [,33]     [,34]     [,35]
> g1  4.030772  4.139881  7.819120  6.665861  6.029291  4.210983  5.805232
> g2 -5.848538 -6.913749 -4.974283 -4.819626 -6.451519 -5.183172 -6.926450
> g3 15.150180 12.122705 12.318756  9.774321 12.053900 12.804219 13.150973
> g4  2.767214  7.031980  3.340560  2.839373  5.854755  4.845936  3.548517
> g5 15.363751 13.055144 11.638995 12.330200 13.551287 14.079976 10.120026
> g6  6.081726  5.163178  4.345026  5.287792  4.039886  4.268287  4.719486
>        [,36]     [,37]      [,38]     [,39]     [,40]     [,41]     [,42]
> g1  5.191718  6.791679  0.8663146  3.496024  7.540578  4.157317  5.824967
> g2 -3.965078 -5.418903 -3.2889290 -3.853233 -5.249636 -4.708381 -3.852609
> g3 10.102709  9.839332 13.1960730 13.043528 12.128328 15.957432  9.885263
> g4  2.747237  2.713851  5.0403970  5.477246  5.926414  3.963112  4.950923
> g5 10.367947 12.536852 16.2168682 13.959325 12.952757 10.846735 11.828050
> g6  6.416214  6.520955  7.6693907  6.130566  6.999619  3.215165  6.309159
>        [,43]     [,44]     [,45]     [,46]     [,47]     [,48]     [,49]
> g1  4.251877  4.671815  6.520268  6.010180  4.914425  4.880138  7.462749
> g2 -2.291497 -5.936301 -7.288554 -3.418578 -4.670871 -5.964936 -6.467616
> g3 10.309409 12.758728 12.679231 14.663813 12.013502 10.610846 11.998989
> g4  3.049874  2.336071  4.609519  3.797285  2.778579  5.707203  2.386412
> g5 12.992869  9.691306 12.678527 11.849048 12.957678 14.498098 12.483435
> g6  5.562398  4.456835  5.657126  6.936155  5.025225  4.952681  5.854294
>        [,50]     [,51]     [,52]     [,53]     [,54]     [,55]     [,56]
> g1  3.279649  8.155739  3.328837  5.966202  7.066623  7.364060  6.666783
> g2 -2.525752 -5.430796 -3.572376 -5.021118 -6.907769 -8.579853 -4.565285
```

```
> g3 13.726523 13.026207 11.991730 11.626853 12.806639 10.493315 10.755663
> g4  4.849554  2.708496  2.660699  3.547060  1.398667  1.798154  6.078243
> g5 11.774445 13.782221 13.047276 12.738766 13.021725 12.639102 14.657278
> g6  4.993505  5.827253  5.985431  4.007061  5.742139  3.291529  4.878911
>         [,57]     [,58]     [,59]     [,60]     [,61]     [,62]     [,63]
> g1  4.608569  9.565325  5.617740  3.280264  6.167656  7.443397  2.717420
> g2 -3.671718 -5.867550 -4.926978 -6.467787 -4.531503 -5.513644 -4.098947
> g3 14.546854 12.285878 13.245295 14.367303 11.268526 13.204385 13.782537
> g4  4.383711  2.030619  5.935189  6.266267  5.102167  4.697446  7.829780
> g5 15.450714 10.135087 15.356626 12.328325 14.748132 15.928337 15.110274
> g6  6.337813  6.974271  7.287177  4.198165  5.660405  6.592660  7.252976
>         [,64]     [,65]     [,66]     [,67]     [,68]     [,69]     [,70]
> g1  6.133300  6.805765  4.799934  3.459253  3.713822  6.306619  5.855048
> g2 -6.431388 -4.230448 -4.235299 -6.096518 -5.932067 -6.085409 -6.371661
> g3 13.657071 11.261520 15.505464 11.609306 13.359181 13.671438 12.239561
> g4  1.886825  3.800876  5.338067  6.023265  4.182496  2.491789  2.645952
> g5 12.736134 12.871195 12.442088 12.959301 14.420964 12.526904 11.310824
> g6  5.373285  6.087010  4.914294  8.209590  5.040481  3.518786  6.247678
>         [,71]     [,72]     [,73]     [,74]     [,75]     [,76]     [,77]
> g1  5.350180  6.972637  2.789593  6.395988  8.723630  6.809106  3.018737
> g2 -3.698488 -5.125613 -2.672631 -5.567265 -4.571688 -7.737190 -4.325746
> g3 11.800124 10.436220 13.387774 13.729736 11.065838 12.025997 11.109470
> g4  3.078969  3.133475  6.181243  1.771083  3.643761  3.823266  8.101476
> g5 13.440260 10.596417 14.030578  9.550747 11.176542 14.799505 13.522736
> g6  8.031478  6.590515  4.976268  4.193635  5.444491  5.704200  6.360672
>         [,78]     [,79]     [,80]     [,81]     [,82]     [,83]     [,84]
> g1  5.014719  6.254796  4.661881  3.426978  5.778662  6.031140  4.277795
> g2 -3.377904 -5.717780 -5.916531 -5.627116 -5.338861 -4.641959 -5.009539
> g3 12.957662 12.866747 13.731911 15.253275 13.158957 13.330229 11.182212
> g4  4.564626  4.348574  4.906275  4.142406  2.648206  2.217461  5.782509
> g5 13.899746 12.218017 13.044694 10.349972 13.443396 13.401074 13.843318
> g6  7.026914  6.462717  5.550402  4.083566  6.956802  6.847857  4.629693
>         [,85]     [,86]     [,87]     [,88]     [,89]      [,90]     [,91]
> g1  5.929004  5.360501  4.159277  6.180398  7.955086  4.7419860  4.267733
> g2 -4.067048 -5.420786 -4.858282 -2.903871 -6.712086 -4.9790215 -2.857574
> g3 13.654184  9.903246 12.290261 12.592012 13.958328 12.1497032 14.519772
> g4  2.501458  3.631767  4.456791  1.000838  3.811322  0.9300523  5.526638
> g5 16.040127 12.929347 13.488692 12.464254  9.996688 12.9422403 12.842729
> g6  7.661532  7.555410  7.216517  5.580799  4.366277  3.9013840  4.141406
>         [,92]     [,93]     [,94]     [,95]     [,96]     [,97]     [,98]
> g1  2.196432  5.468574  4.225360  5.152461  7.692857  4.618577  4.661017
> g2 -3.260505 -6.105861 -6.874641 -4.316166 -5.933591 -3.264276 -4.026105
> g3 13.475219 11.017167 12.231732 12.637023 11.915346 14.893650 11.569158
> g4  5.366747  5.004263  4.140156  3.248260  3.173954  5.322108  5.347235
> g5 13.046375 12.921870 14.754849 13.712662 13.623674 12.535446 11.838365
> g6  6.551831  7.075802  8.551880  5.135304  6.341616  7.113783  6.574019
>         [,99]    [,100]
> g1  5.405681  4.370599
> g2 -5.905981 -6.263881
> g3 13.045248 15.832479
> g4  6.615057  3.889174
> g5 14.112439 12.324249
> g6  6.077500  4.761663
```

```
head(data$Data$Y[[2]])
>           [,1]      [,2]       [,3]      [,4]      [,5]      [,6]      [,7]
> g1 -0.6688194 -5.348649 -2.0843986 -3.178713 -1.581028 -3.253113 -3.214081
> g2  6.7519931  8.195511  5.9706410  9.064598  7.876632  7.122188  6.791217
> g3 15.4198221 17.312380 17.1010765 14.099222 14.130727 16.765843 15.279483
> g4  4.1358360  1.565397  0.5683226  3.570266  3.127495  2.462662  1.610315
> g5  8.4838662  8.595328  7.6138204  8.646461  8.214553  9.297805  8.553389
> g6 -1.2596332  1.412570 -1.0781485  2.065527  1.862148 -0.195726  2.743045
>           [,8]       [,9]     [,10]       [,11]     [,12]      [,13]
> g1 -1.7294123 -0.9435716 -1.972983 -0.73460096 -4.191194 -1.1175961
> g2  4.9149437  6.4826430  7.535674  7.02869647  7.808377  8.1240919
> g3 15.8795828 14.9336174 14.611821 17.60413321 15.282176 13.4479866
> g4  0.9092273  1.2732325  3.564524 -0.00714094  3.823468  1.1488468
> g5  9.6572525 11.0755019 11.209927  8.37726395  9.241613  9.0561967
> g6  1.1671826 -1.2750402  2.981359  2.15097429  2.221589  0.5559568
>          [,14]      [,15]     [,16]      [,17]      [,18]      [,19]
> g1 -0.6713048 -2.8199956 -4.231922 -1.0390592 -0.8302227 -1.6312526
> g2  9.8860678  7.6278161  5.357778  8.4333769  5.6097262  4.5230436
> g3 14.6171172 16.5401871 16.895775 14.5770376 15.9921239 16.3072470
> g4  0.5024050  0.2847666  2.151027  0.9617468  0.8768127  0.7681114
> g5 10.3838587  8.5300117  8.688479 10.6809637  8.4865498  8.6368202
> g6  3.4799285 -0.6710387  1.294831  2.7593473  2.5221879 -1.4062230
>         [,20]     [,21]      [,22]     [,23]     [,24]      [,25]     [,26]
> g1 -2.836041 -1.293572 -3.6554389 -2.270258 -1.669972 -2.6567543 -3.716218
> g2  9.400610  5.452861  4.8582526  4.942723  6.387436  8.6101991  6.462105
> g3 15.551086 15.888116 16.7994775 15.181521 15.438324 17.3774340 14.514816
> g4  3.416110  2.033654  0.8951992  3.382397  3.847197 -0.1681928  1.692522
> g5  9.937879  7.427564  8.7760758 10.135253  9.474181  7.5455453  7.276527
> g6  2.184703  1.303989  1.4837613  0.389393  1.125516 -0.1470143  3.613133
>         [,27]     [,28]      [,29]      [,30]      [,31]      [,32]
> g1 -2.482053 -2.320587 -2.4840779 -2.9460091 -2.5772656 -2.4838471
> g2  7.887218  7.919288  7.9401710  6.7637042  5.3716410  9.1517614
> g3 15.402203 16.042201 15.8029401 16.0479821 16.5772325 17.7154507
> g4 -1.669677  1.352582  0.4339439  3.4398581  1.8424221  2.7331879
> g5  7.898257  8.116908  9.9325564  9.9982059  9.5584083 10.1992229
> g6  1.649434 -0.514661  1.1502570 -0.0254913  0.8675564  0.6279364
>         [,33]      [,34]      [,35]      [,36]      [,37]      [,38]
> g1 -3.230876 -3.2024810 -0.8824972 -0.2224840 -1.6953654 -1.4706263
> g2  5.297643  6.8076381  8.0876338  8.7785111  6.5485590  7.6665722
> g3 19.267041 16.6751397 14.0139489 17.2316606 16.4190603 15.0807396
> g4  1.895821  1.3274477  1.4759512 -0.7036712  0.8480367  1.1647630
> g5  7.468564  7.1669806  8.2719424  7.2392163  8.9830668  7.2075306
> g6 -1.637399  0.8733464  2.1142070 -0.4267469  0.6591673 -0.7652788
>          [,39]      [,40]     [,41]      [,42]     [,43]     [,44]
> g1 -1.3953977 -2.9476054 -1.607573 -3.5240884 -2.455694 -2.005377
> g2  5.7823596  6.9746558  9.137810  6.6624599  6.852136  6.638949
> g3 17.8763792 15.6027575 14.293350 13.7834604 15.328744 15.371321
> g4  1.5046022  1.6076060  3.371372  1.9508356  2.549564  1.528189
> g5  9.7176033 10.0247300  8.234109  9.4782465  8.304556  9.596549
> g6  0.5557341  0.2503158  3.138460 -0.4570873 -1.457600  1.060743
>         [,45]     [,46]      [,47]      [,48]     [,49]      [,50]
> g1 -2.027020 -2.366842 -0.4054931  0.3806541 -3.025950 -3.2017134
> g2  9.032126  5.761622  7.8865326  4.8972871  8.201653  6.9137480
```

```
> g3 13.453900 15.750996 15.0140084 16.0082347 13.694256 17.1571327
> g4  2.389271  2.715015 -0.8355842  1.4973365  1.242229 -0.5439371
> g5  8.701184  9.700740  9.1357881  9.9773668  9.506517 10.3981752
> g6  1.193730  1.181295  1.0138728  1.0664669  2.594850 -1.1429226
>         [,51]      [,52]      [,53]     [,54]      [,55]     [,56]
> g1 -1.924504 -2.2658422 -3.8508420 -2.508271 -4.3843285 -3.916092
> g2  5.699962  5.9046406  7.8412698  6.132090  7.0012165  6.538409
> g3 16.078035 14.9169031 17.7115798 15.426331 20.5217538 17.433260
> g4  3.843953  2.8991367  1.4205417  2.331278  2.5595206  2.661030
> g5  9.101246  8.3177212  7.3752524  7.611848 11.1109515  9.760314
> g6  1.690934 -0.1374805  0.7753557 -1.567144  0.2861129  2.592205
>         [,57]     [,58]     [,59]      [,60]     [,61]      [,62]     [,63]
> g1 -5.165635 -1.614470 -1.138136 -2.9860970 -1.834586 -2.5027261 -4.485998
> g2  7.745257  9.305869  7.681086  7.8050227  5.426266  6.3207609  5.548432
> g3 18.390416 16.006389 15.272950 15.8650980 16.986965 14.9203653 17.403763
> g4  4.279236  2.251574  1.067165  1.2089112  3.856126  3.6464210  3.217647
> g5 11.284779 10.143456 12.323738  7.6792351 10.538798 10.9218143  9.408105
> g6 -0.175259  3.180492  3.022922  0.1630109  1.113622  0.8368243 -1.585782
>          [,64]      [,65]      [,66]     [,67]     [,68]     [,69]
> g1 -1.9538909 -1.6875529 -0.9759211 -4.775772 -2.277033 -1.799255
> g2  5.7185964  5.2695883  6.1918809  7.491361  7.666025  4.958904
> g3 19.8127158 15.9945315 16.0459181 17.823366 14.322770 15.051683
> g4  0.9775788  2.9918660  0.8506442  3.571567  1.551139  2.836274
> g5 10.0864880 10.2248167  8.1130626  9.204385  9.429769  9.513825
> g6 -0.8617533  0.1108613  2.3319359 -0.692288  1.401452  1.184494
>          [,70]      [,71]      [,72]      [,73]     [,74]     [,75]
> g1 -3.2938728 -1.1620814 -5.5006396 -2.2717540 -2.315461 -1.667073
> g2  6.2309281  6.9075569  6.0220919  7.4850511  6.504016  7.287965
> g3 16.3721213 18.0907453 18.0617388 16.5120602 18.401098 12.800086
> g4  4.3776116 -0.8126344  2.8831118  2.1339337  3.079260  2.378615
> g5 11.8852623  9.3307272  7.3405717  9.2875521  6.580681  8.437215
> g6  0.6973231 -1.8735611  0.6776922  0.6958355 -0.631623  1.533989
>         [,76]      [,77]     [,78]      [,79]     [,80]     [,81]     [,82]
> g1 -1.283338 -3.5173984 -2.986830 -2.2400959 -2.987865 -2.438465 -1.762707
> g2  8.101443  8.0872108  6.850441  8.7892851  7.617105  7.142086  7.684555
> g3 15.210425 15.6772821 16.294966 17.0055075 15.733841 17.175957 18.124438
> g4  1.762344  2.3257750  1.060164  5.1511738  1.179494  2.683423  3.695692
> g5  9.009134  8.6348090  5.927795  9.4753915 10.690916 12.141942 12.476967
> g6 -1.070067 -0.3018053 -1.500406  0.7219533  1.385052  3.513559  0.664869
>          [,83]      [,84]     [,85]      [,86]     [,87]      [,88]
> g1 -2.8087724 -1.1927739 -4.303364 -1.5334135 -3.846641 -5.1684704
> g2  4.1017950  5.5777615  4.854949  5.4239694  6.461510  8.3679369
> g3 18.6930431 16.1595262 17.147868 15.0944065 16.377274 14.1539928
> g4  0.2003213  1.2966241  1.586223  0.2276401  3.030830  3.4054644
> g5 10.5747200  7.6824653  8.216395  7.9562279  7.318216  9.0150065
> g6  1.6055047  0.1434489  2.110119  1.3918317 -2.152979  0.1541954
>          [,89]     [,90]     [,91]     [,92]      [,93]     [,94]     [,95]
> g1 -1.5354540 -3.743334 -3.264888 -1.925454 -1.8202762 -1.339498 -1.548623
> g2  5.6516265  6.216713  5.354513  6.093214  7.2297233  6.808957  6.911173
> g3 14.7065212 14.467238 16.369987 15.598423 18.0663333 14.387333 14.760238
> g4  0.6788600  3.602734  2.210013  3.773766  1.0022826  1.426318  1.701595
> g5  7.4198509  9.364366  7.419709  8.632720  9.3381134 10.003613 10.130469
> g6 -0.2466479  2.101646 -1.053596  2.652695 -0.7299923  3.495239  1.539921
```

```
>          [,96]      [,97]      [,98]     [,99]     [,100]
> g1 -0.8804441 -2.3773340 -1.4753953 -3.867311 -0.3535292
> g2  5.8432919  5.9827687  5.7165355  5.914354  5.5842416
> g3 17.0017184 17.2261065 18.2708674 16.602639 16.0129119
> g4  0.2978405  1.8030734  2.2866208  5.396393  2.4744446
> g5  7.0284032  7.2024455  8.8490523  9.375925 10.3587815
> g6 -0.2529803 -0.1748777 -0.9360543 -1.198418  2.2489009
```

2. 60 corresponding cis-eQTLs' genotype under two conditions

```
head(data$Data$X[[1]] - 1)
>     [,1] [,2] [,3] [,4] [,5] [,6] [,7] [,8] [,9] [,10] [,11] [,12] [,13]
> rs1    1    0    0    1    1    0    1    0    1     1     2     1     0
> rs2    1    0    0    2    0    0    1    0    1     2     1     1     2
> rs3    0    1    0    0    0    1    1    0    2     1     2     1     1
> rs4    1    2    1    1    1    1    1    2    2     2     1     1     0
> rs5    0    1    1    1    1    2    1    1    1     1     1     1     1
> rs6    0    0    0    1    1    2    0    2    1     0     0     1     1
>     [,14] [,15] [,16] [,17] [,18] [,19] [,20] [,21] [,22] [,23] [,24]
> rs1     1     1     2     1     1     0     0     1     2     2     0
> rs2     0     1     1     2     0     0     2     1     2     1     2
> rs3     0     1     0     1     1     1     1     1     0     1     0
> rs4     1     2     1     1     1     2     1     1     1     1     0
> rs5     2     1     0     2     1     1     1     1     0     1     1
> rs6     2     0     2     1     1     2     1     1     2     0     0
>     [,25] [,26] [,27] [,28] [,29] [,30] [,31] [,32] [,33] [,34] [,35]
> rs1     2     1     1     1     0     1     1     1     1     0     1
> rs2     1     1     2     0     0     1     1     2     0     1     1
> rs3     1     1     2     2     2     1     1     1     2     0     2
> rs4     1     2     2     1     1     2     0     1     1     0     0
> rs5     1     1     2     1     1     1     2     1     1     1     1
> rs6     0     2     1     0     0     1     1     1     0     0     1
>     [,36] [,37] [,38] [,39] [,40] [,41] [,42] [,43] [,44] [,45] [,46]
> rs1     1     1     0     1     2     0     1     2     0     2     1
> rs2     1     1     2     2     1     1     1     2     1     0     2
> rs3     0     1     0     0     0     1     0     0     1     1     2
> rs4     0     1     1     1     1     0     2     1     0     1     2
> rs5     0     1     2     1     1     0     0     1     1     0     1
> rs6     1     1     2     2     1     0     1     1     0     2     2
>     [,47] [,48] [,49] [,50] [,51] [,52] [,53] [,54] [,55] [,56] [,57]
> rs1     1     0     1     0     2     1     1     2     2     2     1
> rs2     1     0     2     2     0     2     2     0     0     1     1
> rs3     1     0     0     0     1     1     0     1     1     2     1
> rs4     1     1     1     1     1     0     1     1     0     2     1
> rs5     1     0     1     1     2     1     1     1     1     1     1
> rs6     0     1     1     1     2     2     1     2     0     1     1
>     [,58] [,59] [,60] [,61] [,62] [,63] [,64] [,65] [,66] [,67] [,68]
> rs1     2     2     1     1     1     1     0     0     2     1     0
> rs2     1     2     2     0     1     1     0     1     2     1     2
> rs3     1     2     2     2     0     0     1     1     2     1     0
> rs4     2     1     1     2     1     2     0     1     1     2     2
> rs5     0     1     0     2     2     1     1     1     1     0     2
> rs6     2     2     1     1     1     1     1     1     1     2     1
>     [,69] [,70] [,71] [,72] [,73] [,74] [,75] [,76] [,77] [,78] [,79]
```

```
> rs1     1     1     1     2     0     1     2     1     1     1     1
> rs2     1     1     1     1     2     0     2     1     2     2     1
> rs3     1     1     1     1     1     2     1     1     1     1     1
> rs4     0     0     2     1     2     0     1     1     2     2     2
> rs5     1     0     0     1     1     0     1     1     1     1     1
> rs6     0     1     2     1     1     1     1     0     1     1     1
>     [,80] [,81] [,82] [,83] [,84] [,85] [,86] [,87] [,88] [,89] [,90]
> rs1     1     1     1     0     0     2     1     1     1     2     1
> rs2     1     1     0     1     0     1     0     1     2     1     1
> rs3     2     1     1     2     0     1     0     2     2     0     1
> rs4     1     1     1     1     2     0     1     1     1     2     0
> rs5     1     0     2     1     0     2     0     2     1     0     2
> rs6     1     1     1     0     0     2     1     1     1     1     0
>     [,91] [,92] [,93] [,94] [,95] [,96] [,97] [,98] [,99] [,100]
> rs1     2     0     1     0     2     1     0     1     1      1
> rs2     1     2     1     1     2     1     1     1     2      0
> rs3     2     0     0     0     2     1     2     1     1      2
> rs4     2     1     2     2     0     1     1     1     2      1
> rs5     2     0     1     2     2     1     0     0     1      1
> rs6     1     1     2     2     1     1     2     0     2      0
head(data$Data$X[[2]] - 1)
>     [,1] [,2] [,3] [,4] [,5] [,6] [,7] [,8] [,9] [,10] [,11] [,12] [,13]
> rs1    1    0    2    1    1    1    1    2    1     2     2     2     0
> rs2    0    2    2    2    2    1    0    1    1     1     1     1     1
> rs3    1    1    1    1    0    2    1    2    1     1     2     0     0
> rs4    2    0    0    2    1    1    2    1    1     2     1     1     1
> rs5    0    1    1    1    0    1    2    1    2     1     1     1     1
> rs6    0    2    0    0    1    1    2    1    0     2     1     1     0
>     [,14] [,15] [,16] [,17] [,18] [,19] [,20] [,21] [,22] [,23] [,24]
> rs1     2     0     1     1     0     1     1     2     0     1     1
> rs2     1     1     1     1     0     0     1     1     0     0     0
> rs3     0     1     1     1     1     2     1     1     1     1     2
> rs4     1     0     1     1     2     1     1     2     1     2     1
> rs5     1     1     1     1     0     1     1     2     1     1     1
> rs6     2     0     2     1     2     0     1     2     2     1     2
>     [,25] [,26] [,27] [,28] [,29] [,30] [,31] [,32] [,33] [,34] [,35]
> rs1     1     0     0     1     0     2     0     0     1     2     1
> rs2     2     1     1     1     1     1     0     2     0     2     2
> rs3     1     0     1     2     1     0     2     2     2     1     0
> rs4     1     1     0     0     1     2     2     2     1     1     1
> rs5     1     1     1     0     1     1     2     1     1     0     1
> rs6     1     2     2     1     0     1     1     1     1     1     2
>     [,36] [,37] [,38] [,39] [,40] [,41] [,42] [,43] [,44] [,45] [,46]
> rs1     1     1     2     1     0     1     0     1     1     2     1
> rs2     1     0     2     0     1     1     1     0     0     2     0
> rs3     1     1     2     2     1     1     1     1     1     0     1
> rs4     1     1     0     1     0     1     1     1     1     1     0
> rs5     0     1     0     1     1     0     2     2     1     0     0
> rs6     0     0     1     0     0     2     1     1     1     1     1
>     [,47] [,48] [,49] [,50] [,51] [,52] [,53] [,54] [,55] [,56] [,57]
> rs1     2     2     0     1     1     0     0     2     1     1     0
> rs2     1     0     2     2     1     1     2     1     1     1     2
> rs3     0     1     0     1     1     1     2     0     2     1     2
```

```
> rs4      0     1     0     1     1     0     1     2     1     2     2
> rs5      1     1     2     2     2     1     1     0     2     1     1
> rs6      1     0     1     0     1     1     1     0     1     1     1
>      [,58] [,59] [,60] [,61] [,62] [,63] [,64] [,65] [,66] [,67] [,68]
> rs1      2     2     0     1     1     0     2     0     1     0     1
> rs2      2     1     1     1     1     0     1     0     1     1     1
> rs3      1     1     1     2     1     1     2     1     1     2     0
> rs4      1     1     2     1     1     1     1     0     2     1     0
> rs5      1     2     1     2     2     0     2     2     1     1     1
> rs6      1     1     0     2     1     1     0     1     1     0     2
>      [,69] [,70] [,71] [,72] [,73] [,74] [,75] [,76] [,77] [,78] [,79]
> rs1      0     2     0     0     1     2     2     2     1     1     0
> rs2      1     1     0     1     0     1     2     2     0     1     2
> rs3      1     2     1     1     1     2     0     2     2     0     1
> rs4      2     2     0     1     2     2     1     1     1     1     2
> rs5      1     2     1     2     1     0     1     1     1     1     0
> rs6      0     1     0     1     1     1     0     1     1     0     1
>      [,80] [,81] [,82] [,83] [,84] [,85] [,86] [,87] [,88] [,89] [,90]
> rs1      0     1     2     1     1     0     1     0     0     1     1
> rs2      1     0     2     0     1     1     0     1     1     1     0
> rs3      0     1     1     1     2     1     0     2     0     1     0
> rs4      2     1     1     0     1     1     1     2     2     1     2
> rs5      2     2     2     0     0     0     1     0     2     0     0
> rs6      1     2     1     1     1     1     2     0     1     0     2
>      [,91] [,92] [,93] [,94] [,95] [,96] [,97] [,98] [,99] [,100]
> rs1      2     2     0     2     1     1     1     1     0      2
> rs2      0     1     2     1     1     1     1     1     0      0
> rs3      1     0     2     0     1     2     1     1     1      1
> rs4      1     1     1     0     2     0     0     0     2      1
> rs5      0     2     1     1     1     1     1     1     1      0
> rs6      1     2     1     1     1     0     1     0     0      2
```

3. `data$Data$Sk` stores each gene's cis-eQTL's indices. In real data application, we recommend to use package `MatrixEQTL` to search the significant cis-eQTLs for genes of interested and build `Sk` for your research

```
head(data$Data$Sk)
> $g1
> [1]  1 21 41
>
> $g2
> [1]  2 22 42
>
> $g3
> [1]  3 23 43
>
> $g4
> [1]  4 24 44
>
> $g5
> [1]  5 25 45
>
> $g6
> [1]  6 26 46
```

Initialization of `fssemR` by ridge regression

We implement our fssemR by the observed gene expression data and genetic perturbations data that stored in `data$Data`, and it is initialized by ridge regression, the l_2 norm penalty's hyperparameter γ is selected by 5-fold cross-validation.

```
Xs  = data$Data$X     ## eQTL's genotype data
Ys  = data$Data$Y     ## gene expression data
Sk  = data$Data$Sk    ## cis-eQTL indices
gamma = cv.multiRegression(Xs, Ys, Sk, ngamma = 50, nfold = 5, n = data$Vars$n,
                           p = data$Vars$p, k = data$Vars$k)
>  [1] 17.089156 16.916607 16.716384 16.485561 16.221403 15.921540 15.584162
>  [8] 15.208200 14.793504 14.340949 13.852502 13.331184 12.780976 12.206639
> [15] 11.613515 11.007305 10.393864  9.779057  9.168644  8.568228  7.983236
> [22]  7.418917  6.880334  6.372310  5.899354  5.465477  5.073986  4.727216
> [29]  4.426271  4.170828  3.959063  3.787766  3.652614  3.548598  3.470474
> [36]  3.413183  3.372149  3.343459  3.323905  3.310962  3.302696  3.297671
> [43]  3.294839  3.293454  3.292996  3.293105  3.293540  3.294144  3.294815
> [50]  3.295488
fit0   = multiRegression(data$Data$X, data$Data$Y, data$Data$Sk, gamma, trans = FALSE,
                         n = data$Vars$n, p = data$Vars$p, k = data$Vars$k)
```

Run fssemR algorithm for data

Then, we chose the `fit0` object from ridge regression as intialization, and implement the `fssemR` algorithm, BIC is used to select optimal hyperparameters λ, ρ, where `nlambda` is the number of candidate lambda values for l_1 regularized term, and `nrho` is the number of candidate rho values for fused lasso regularized term.

```
fitOpt <- opt.multiFSSEMiPALM2(Xs = Xs, Ys = Ys, Bs = fit0$Bs, Fs = fit0$Fs, Sk = Sk,
                               sigma2 = fit0$sigma2, nlambda = 10, nrho = 10,
                               p = data$Vars$p, q = data$Vars$k, wt = TRUE)
> FSSEM@lambda = 96.991109, rho = 0.000000
> FSSEM@lambda = 96.991109, rho = 0.000000
> FSSEM@lambda = 96.991109, rho = 0.000000
> FSSEM@lambda = 96.991109, rho = 0.000000
> FSSEM@lambda = 96.991109, rho = 0.000000
> FSSEM@lambda = 96.991109, rho = 0.000000
> FSSEM@lambda = 96.991109, rho = 0.000000
> FSSEM@lambda = 96.991109, rho = 0.000000
> FSSEM@lambda = 96.991109, rho = 0.000000
> FSSEM@lambda = 96.991109, rho = 0.000000
> FSSEM@lambda = 45.019285, rho = 3.521128
> FSSEM@lambda = 45.019285, rho = 1.634363
> FSSEM@lambda = 45.019285, rho = 0.758604
> FSSEM@lambda = 45.019285, rho = 0.352113
> FSSEM@lambda = 45.019285, rho = 0.163436
> FSSEM@lambda = 45.019285, rho = 0.075860
> FSSEM@lambda = 45.019285, rho = 0.035211
> FSSEM@lambda = 45.019285, rho = 0.016344
> FSSEM@lambda = 45.019285, rho = 0.007586
> FSSEM@lambda = 45.019285, rho = 0.003521
> FSSEM@lambda = 20.896101, rho = 4.273226
> FSSEM@lambda = 20.896101, rho = 1.983456
> FSSEM@lambda = 20.896101, rho = 0.920639
```

```
> FSSEM@lambda = 20.896101, rho = 0.427323
> FSSEM@lambda = 20.896101, rho = 0.198346
> FSSEM@lambda = 20.896101, rho = 0.092064
> FSSEM@lambda = 20.896101, rho = 0.042732
> FSSEM@lambda = 20.896101, rho = 0.019835
> FSSEM@lambda = 20.896101, rho = 0.009206
> FSSEM@lambda = 20.896101, rho = 0.004273
> FSSEM@lambda = 9.699111, rho = 4.480254
> FSSEM@lambda = 9.699111, rho = 2.079550
> FSSEM@lambda = 9.699111, rho = 0.965241
> FSSEM@lambda = 9.699111, rho = 0.448025
> FSSEM@lambda = 9.699111, rho = 0.207955
> FSSEM@lambda = 9.699111, rho = 0.096524
> FSSEM@lambda = 9.699111, rho = 0.044803
> FSSEM@lambda = 9.699111, rho = 0.020795
> FSSEM@lambda = 9.699111, rho = 0.009652
> FSSEM@lambda = 9.699111, rho = 0.004480
> FSSEM@lambda = 4.501929, rho = 223.771520
> FSSEM@lambda = 4.501929, rho = 103.865539
> FSSEM@lambda = 4.501929, rho = 48.210113
> FSSEM@lambda = 4.501929, rho = 22.377152
> FSSEM@lambda = 4.501929, rho = 10.386554
> FSSEM@lambda = 4.501929, rho = 4.821011
> FSSEM@lambda = 4.501929, rho = 2.237715
> FSSEM@lambda = 4.501929, rho = 1.038655
> FSSEM@lambda = 4.501929, rho = 0.482101
> FSSEM@lambda = 4.501929, rho = 0.223772
> FSSEM@lambda = 2.089610, rho = 334.212580
> FSSEM@lambda = 2.089610, rho = 155.127738
> FSSEM@lambda = 2.089610, rho = 72.003918
> FSSEM@lambda = 2.089610, rho = 33.421258
> FSSEM@lambda = 2.089610, rho = 15.512774
> FSSEM@lambda = 2.089610, rho = 7.200392
> FSSEM@lambda = 2.089610, rho = 3.342126
> FSSEM@lambda = 2.089610, rho = 1.551277
> FSSEM@lambda = 2.089610, rho = 0.720039
> FSSEM@lambda = 2.089610, rho = 0.334213
> FSSEM@lambda = 0.969911, rho = 453.396931
> FSSEM@lambda = 0.969911, rho = 210.448213
> FSSEM@lambda = 0.969911, rho = 97.681408
> FSSEM@lambda = 0.969911, rho = 45.339693
> FSSEM@lambda = 0.969911, rho = 21.044821
> FSSEM@lambda = 0.969911, rho = 9.768141
> FSSEM@lambda = 0.969911, rho = 4.533969
> FSSEM@lambda = 0.969911, rho = 2.104482
> FSSEM@lambda = 0.969911, rho = 0.976814
> FSSEM@lambda = 0.969911, rho = 0.453397
> FSSEM@lambda = 0.450193, rho = 443.637707
> FSSEM@lambda = 0.450193, rho = 205.918383
> FSSEM@lambda = 0.450193, rho = 95.578847
> FSSEM@lambda = 0.450193, rho = 44.363771
> FSSEM@lambda = 0.450193, rho = 20.591838
> FSSEM@lambda = 0.450193, rho = 9.557885
```

```
> FSSEM@lambda = 0.450193, rho = 4.436377
> FSSEM@lambda = 0.450193, rho = 2.059184
> FSSEM@lambda = 0.450193, rho = 0.955788
> FSSEM@lambda = 0.450193, rho = 0.443638
> FSSEM@lambda = 0.208961, rho = 393.824671
> FSSEM@lambda = 0.208961, rho = 182.797219
> FSSEM@lambda = 0.208961, rho = 84.846953
> FSSEM@lambda = 0.208961, rho = 39.382467
> FSSEM@lambda = 0.208961, rho = 18.279722
> FSSEM@lambda = 0.208961, rho = 8.484695
> FSSEM@lambda = 0.208961, rho = 3.938247
> FSSEM@lambda = 0.208961, rho = 1.827972
> FSSEM@lambda = 0.208961, rho = 0.848470
> FSSEM@lambda = 0.208961, rho = 0.393825
> FSSEM@lambda = 0.096991, rho = 369.073646
> FSSEM@lambda = 0.096991, rho = 171.308811
> FSSEM@lambda = 0.096991, rho = 79.514507
> FSSEM@lambda = 0.096991, rho = 36.907365
> FSSEM@lambda = 0.096991, rho = 17.130881
> FSSEM@lambda = 0.096991, rho = 7.951451
> FSSEM@lambda = 0.096991, rho = 3.690736
> FSSEM@lambda = 0.096991, rho = 1.713088
> FSSEM@lambda = 0.096991, rho = 0.795145
> FSSEM@lambda = 0.096991, rho = 0.369074

fit <- fitOpt$fit
```

Comparing our estimated GRNs and differential GRN with ground truth

```
cat("Power of two estimated GRNs = ",
    (TPR(fit$Bs[[1]], data$Vars$B[[1]]) + TPR(fit$Bs[[2]], data$Vars$B[[2]])) / 2)
> Power of two estimated GRNs =  1
cat("FDR of two estimated GRNs = ",
    (FDR(fit$Bs[[1]], data$Vars$B[[1]]) + FDR(fit$Bs[[2]], data$Vars$B[[2]])) / 2)
> FDR of two estimated GRNs =  0
cat("Power of estimated differential GRN = ",
    TPR(fit$Bs[[1]] - fit$Bs[[2]], data$Vars$B[[1]] - data$Vars$B[[2]]))
> Power of estimated differential GRN =  1
cat("FDR of estimated differential GRN = ",
    FDR(fit$Bs[[1]] - fit$Bs[[2]], data$Vars$B[[1]] - data$Vars$B[[2]]))
> FDR of estimated differential GRN =  0.1176471
```

From these 4 metrics, we can get the performance of our `fssemR` algorithm comparing to the ground truth (if we know)

Differential GRN Visualization

```
# data$Vars$B[[2]]    ## simulated GRN under condition 2
diffGRN = network(t(fit$Bs[[2]] - fit$Bs[[1]]) != 0, matrix.type = "adjacency", directed = TRUE)
> <sparse>[ <logic> ] : .M.sub.i.logical() maybe inefficient
# up-regulated edges are colored by `red` and down-regulated edges are colored by `blue`
```

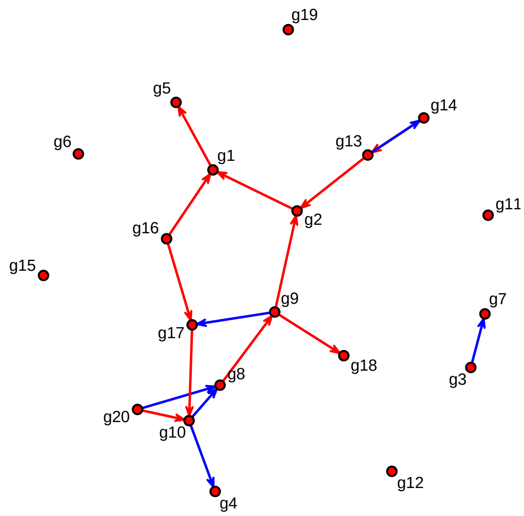

Figure 4: estimated differential GRN by fssemR

```
ecol = 3 - sign(t(fit$Bs[[2]] - fit$Bs[[1]]))
plot(diffGRN, displaylabels = TRUE, label = network.vertex.names(GRN_2), label.cex = 0.5, edge.col = eco
```

Additionally, the differeitial effect of two GRN are also estimated. Therefore, we can tell how the interactions in two GRNs change.

```
diffGRN = Matrix::Matrix(fit$Bs[[1]] - fit$Bs[[2]], sparse = TRUE)
diffGRN
> 20 x 20 sparse Matrix of class "dgCMatrix"
>
>  [1,]  .         -0.2499698 .         0 . . .  .          .
>  [2,]  .          .         .         . . . .  .         -0.3477201
>  [3,]  0.0000000  .         .         . . . .  .          .
>  [4,]  .          .         .         . . . .  .          .
>  [5,] -0.2134709  .         .         0 . . .  .          .
>  [6,]  .          .         0.0000000 . 0 . .  .          .
>  [7,]  0.0000000  .         0.3864315 0 . . .  .          .
>  [8,]  .          .         .         . . . .  .          .
>  [9,]  .          .         .         . . . . -0.3995763  .
> [10,]  .          0.0000000 .         . . . .  .          .
> [11,]  .          .         0.0000000 . . 0 .  .          .
> [12,]  .          .         .         . . . .  .          .
> [13,]  .          .         .         . . . .  .          .
> [14,]  .          .         .         . . . .  .          .
> [15,]  .          .         .         . . . .  .          .
> [16,]  .          .         .         . . . .  .          .
> [17,]  .          .         .         . . . .  .          0.2648751
> [18,]  .          .         .         . . . .  .         -0.3542213
> [19,]  .          0.0000000 .         . . . .  .          .
> [20,]  .          .         .         . . . .  .          .
>
>  [1,] .         . .  .          .         . -0.0103342  .         . .
>  [2,] .         . 0 -0.3927113  .         .  .          .         . .
>  [3,] 0.0000000 . .  .          .         0  .          .         0 .
```

```
>  [4,] 0.2547898 . .  0.0000000  .         .  0.0000000  .         0 .
>  [5,] .         . .  .          .         .  .          .         . 0
>  [6,] .         . .  .          .         .  .          .         . .
>  [7,] 0.0000000 . .  0.0000000  .         .  .          .         0 .
>  [8,] 0.2816496 . .  .          0.0000000 .  0.0000000  .         . .
>  [9,] .         . .  .          .         .  .          .         . .
> [10,] .         . .  .          0.0000000 .  .         -0.3313498 . 0
> [11,] .         . .  .          .         .  .          .         . .
> [12,] .         . .  .          .         .  .          .         . .
> [13,] .         . .  .         -0.2541683 .  .          .         . .
> [14,] .         . .  0.3313431  .         0  .          .         . .
> [15,] .         . .  .          .         .  .          .         . .
> [16,] .         . .  .          0.0000000 .  .          .         . .
> [17,] .         . .  .          .         . -0.3236840  .         . 0
> [18,] .         . .  .          .         .  .          0.0000000 . .
> [19,] .         . 0  .          .         .  .          .         . .
> [20,] .         . .  .          .         .  .          .         . .
> 
>  [1,]  .         
>  [2,]  .         
>  [3,]  .         
>  [4,]  .         
>  [5,]  0.00000000
>  [6,]  .         
>  [7,]  .         
>  [8,]  0.37876759
>  [9,]  .         
> [10,] -0.01249568
> [11,]  .         
> [12,]  .         
> [13,]  0.00000000
> [14,]  0.00000000
> [15,]  .         
> [16,]  .         
> [17,]  .         
> [18,]  .         
> [19,]  0.00000000
> [20,]  .
```

From the diffGRN, we can determined how the gene-gene interactions in GRN changes across two conditions, then, we can find out the key genes for condition-specific gene regulatory network.

Additionally, for more applications and the replications of our real data analysis, please go to the `https://github.com/Ivis4ml/fssemR/tree/master/inst` for more cases.

Session Information

```
sessionInfo()
> R version 3.4.0 (2017-04-21)
> Platform: x86_64-pc-linux-gnu (64-bit)
> Running under: Ubuntu 14.04.6 LTS
> 
> Matrix products: default
```

```
> BLAS: /usr/lib64/microsoft-r/3.4/lib64/R/lib/libRblas.so
> LAPACK: /usr/lib64/microsoft-r/3.4/lib64/R/lib/libRlapack.so
>
> locale:
>  [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
>  [3] LC_TIME=en_US.UTF-8        LC_COLLATE=C
>  [5] LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8
>  [7] LC_PAPER=en_US.UTF-8       LC_NAME=C
>  [9] LC_ADDRESS=C               LC_TELEPHONE=C
> [11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C
>
> attached base packages:
> [1] stats     graphics  grDevices utils     datasets  methods   base
>
> other attached packages:
> [1] Matrix_1.2-14      ggnetwork_0.5.1    ggplot2_3.1.0.9000
> [4] network_1.13.0.1   fssemR_0.1.4
>
> loaded via a namespace (and not attached):
>  [1] Rcpp_1.0.0           sna_2.4              bindr_0.1.1
>  [4] compiler_3.4.0       pillar_1.3.1         iterators_1.0.9
>  [7] tools_3.4.0          digest_0.6.18        evaluate_0.12
> [10] tibble_2.0.1         gtable_0.2.0         lattice_0.20-35
> [13] pkgconfig_2.0.2      rlang_0.3.1          foreach_1.4.4
> [16] igraph_1.2.2         ggrepel_0.8.0        yaml_2.2.0
> [19] parallel_3.4.0       mvtnorm_1.0-8        xfun_0.4
> [22] bindrcpp_0.2.2       coda_0.19-2          withr_2.1.2
> [25] stringr_1.3.1        dplyr_0.7.8          knitr_1.21
> [28] tidyselect_0.2.5     glmnet_2.0-16        grid_3.4.0
> [31] glue_1.3.0           R6_2.2.2             qtl_1.44-9
> [34] rmarkdown_1.11       purrr_0.3.0          magrittr_1.5
> [37] scales_1.0.0.9000    codetools_0.2-15     htmltools_0.3.6
> [40] MASS_7.3-49          assertthat_0.2.0     colorspace_1.4-0
> [43] stringi_1.2.4        lazyeval_0.2.1       munsell_0.5.0
> [46] statnet.common_4.1.4 crayon_1.3.4
```