

# fssemR: Fused Sparse Structural Equation Models to Jointly Infer Gene Regulatory Networks

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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 `randomFSSEMdata2` 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 conclusion, 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)
library(ggnetwork)
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
k = 3                # each gene has nonzero 3 cis-eQTL effect
sigma2 = 0.01        # simulated noise variance
prob = 3              # 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 = 1234          # 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)
```

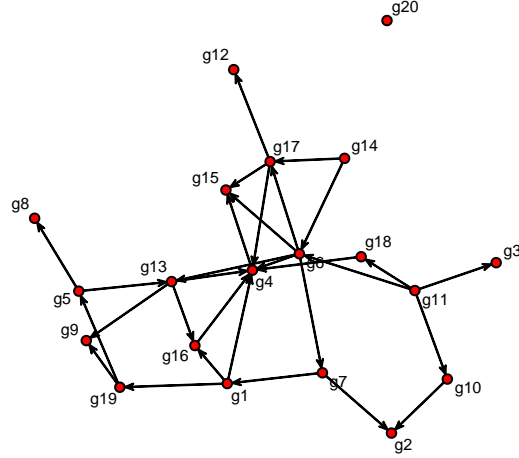


Figure 1: Simulated GRN under condition 1

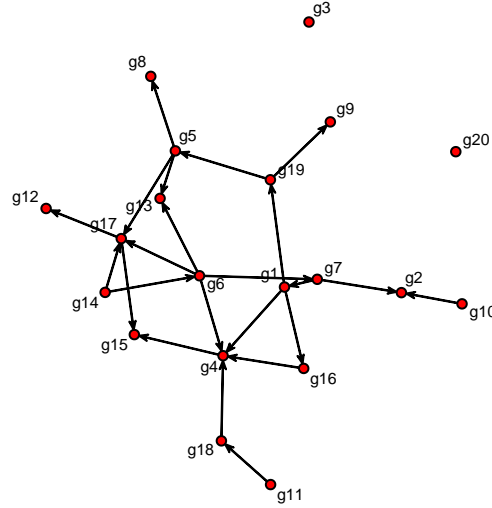


Figure 2: Simulated GRN under condition 2

- 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 = TRUE)
> <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 = ecol)
```



## 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]
> g1	2.770448	6.259964	6.674162	6.808461	5.680147	7.318518
> g2	16.693933	16.400043	17.907393	20.717025	18.462004	19.310053
> g3	-4.143627	-1.537331	-1.487832	-6.339450	-3.506562	-3.625918
> g4	-13.823825	-11.027926	-13.736342	-10.500963	-11.822357	-7.312691
> g5	3.334527	4.691596	1.231610	1.863935	3.921532	1.092439
> g6	11.946279	12.189177	12.592806	9.531924	12.283651	9.101853

	[,7]	[,8]	[,9]	[,10]	[,11]	[,12]
> g1	7.925731	5.469580	6.874138	6.259060	4.991997	3.6558171
> g2	20.064330	18.625910	17.263045	18.031644	17.971561	19.3634073
> g3	-2.821562	-3.989399	-4.372809	-4.848280	-3.273691	-4.9118578
> g4	-10.882462	-11.926105	-9.673294	-11.874307	-13.799269	-11.9793126
> g5	3.386369	3.528428	2.820687	1.429835	2.773986	0.9921462
> g6	10.454074	9.374013	11.899145	11.914369	11.560273	9.3255531

	[,13]	[,14]	[,15]	[,16]	[,17]	[,18]
> g1	9.0770168	5.6315452	6.6524100	7.8541907	2.7487485	3.9887650
> g2	21.5317595	15.9797857	18.7269834	15.6236696	15.2581297	16.8721849
> g3	-3.7886454	-4.9133877	-2.9578181	-2.7955708	-4.1907567	-7.0963695
> g4	-7.1027533	-12.9192965	-10.8718204	-10.2683217	-13.0916818	-12.3372152
> g5	0.4206075	0.2349598	-0.4666022	0.5809634	0.3444712	0.2551614
> g6	8.7646739	10.0190473	12.4381136	11.0151567	11.3150153	11.5710326

	[,19]	[,20]	[,21]	[,22]	[,23]	[,24]
> g1	2.424377	3.139723	5.882116	7.097460	6.4267704	3.5841797
> g2	19.515048	17.469934	17.616417	20.214885	18.7438415	18.9216099
> g3	-3.976164	-1.754099	-4.261824	-3.903713	-4.3920988	-3.5657696
> g4	-9.581770	-11.708551	-9.683074	-12.941502	-10.0141733	-13.5747447
> g5	3.865410	2.042421	1.629456	3.318893	-0.6147502	-0.1247361
> g6	7.782795	10.619403	11.493185	12.700910	11.0183445	11.1710466

	[,25]	[,26]	[,27]	[,28]	[,29]	[,30]
> g1	4.817649	4.7659734	4.89861776	4.622141	2.7658565	4.349978
> g2	18.714211	16.7075823	19.73046183	17.458651	18.8136511	17.162172
> g3	-4.691829	-3.3885190	-3.84873719	-1.869941	-2.6170182	-4.288225
> g4	-11.879677	-11.5629418	-12.19956473	-10.094749	-13.1710101	-10.217128
> g5	2.274330	0.8840928	0.04969382	1.595256	0.8528509	1.651465
> g6	9.396885	10.4390922	10.72582492	12.284884	12.1070376	9.195672

	[,31]	[,32]	[,33]	[,34]	[,35]	[,36]
> g1	3.543636	5.954406	3.907671	5.046753	7.990178	6.327497
> g2	16.878461	19.035679	20.335273	19.003801	21.034857	19.952476
> g3	-1.726678	-3.761303	-4.577775	-6.274101	-2.634423	-5.533067
> g4	-12.532556	-11.581748	-10.914734	-10.954571	-10.224966	-12.476030
> g5	2.662231	1.893884	2.981806	1.274090	1.649356	1.757932
> g6	10.596832	12.681480	9.981001	9.478938	10.343363	13.270179

	[,37]	[,38]	[,39]	[,40]	[,41]	[,42]
> g1	5.720402	3.813243	5.946461	5.888265	3.684659	3.672092
> g2	19.863058	18.437618	16.550861	18.320714	18.209933	18.986330
> g3	-5.587944	-2.793105	-3.958480	-2.841557	-3.885837	-3.955722

```

> g4 -12.073591 -11.487370 -11.252530 -11.105414 -13.445681 -14.351061
> g5  1.070389  -2.169704  3.096173  2.099796  -1.013806  1.311431
> g6 10.340032 12.008636 11.363062 12.055004 10.158709 11.769262
>      [,43]      [,44]      [,45]      [,46]      [,47]      [,48]
> g1  4.5917122  4.295282  6.524264  4.906347  6.536732  4.879435
> g2 17.6616356 19.092571 16.980908 17.926787 20.854698 18.096823
> g3 -4.1945620 -5.919006 -5.307858 -2.065621 -2.911331 -4.558058
> g4 -11.3283471 -13.501180 -10.086630 -9.918077 -9.818009 -11.012461
> g5 -0.9669337  1.025179  2.193783  2.431141  2.891142  2.098039
> g6  9.9449443 12.121816  8.819851 10.539147  8.886218 11.969230
>      [,49]      [,50]      [,51]      [,52]      [,53]      [,54]
> g1  5.805099  5.3481447  6.542402  4.548018  6.5052474  5.6800691
> g2 19.893654 17.1882774 18.428548 20.609397 18.2871916 16.4169909
> g3 -5.709911  -4.9131706 -3.418575  -4.720646 -2.5454282 -3.0046541
> g4 -12.567286 -14.6149848 -10.212645 -13.427252 -8.5490332 -9.3466052
> g5  1.445014  0.7621789  1.626611  0.504638 -0.5208959  0.4608354
> g6 12.931516 12.1752790 11.583177  9.203124 11.0028094  9.1496536
>      [,55]      [,56]      [,57]      [,58]      [,59]      [,60]
> g1  4.812958  4.8661167  4.869438  5.344981  6.20694731  5.5725124
> g2 16.738751 17.9204878 18.189879 16.570016 15.91771238 19.7115401
> g3 -2.779173 -5.5457626 -2.990251 -3.306833 -2.64457257 -3.3681411
> g4 -11.626939 -9.6168655 -9.334655 -10.442561 -9.57074956 -14.3716526
> g5  2.339131  0.1455553  2.476909  1.206455 -0.01564206  0.1179841
> g6 10.106026 10.2269138  9.342599 10.693833  9.69753120 12.2839852
>      [,61]      [,62]      [,63]      [,64]      [,65]      [,66]
> g1  7.342388  6.648037  3.600893  5.336076  4.133792  5.465963
> g2 20.198763 18.900766 16.701180 17.194249 17.942103 15.649900
> g3 -3.813033 -6.186200 -5.873100 -1.879813 -5.503249 -5.839342
> g4 -10.967209 -9.121562 -9.566319 -11.432820 -13.677219 -11.592131
> g5  3.129266  3.658870  3.548002  1.136549 -1.332778  2.128129
> g6 12.412034  8.365781 10.289357 11.048246 11.253684 12.057317
>      [,67]      [,68]      [,69]      [,70]      [,71]      [,72]
> g1  3.1178414  3.040707  6.146053  4.658552  7.422017  4.866166
> g2 19.0049328 17.458261 18.793092 18.685292 20.294841 16.868347
> g3 -4.0496717 -3.996697 -4.685695 -2.634156 -3.524620 -1.687134
> g4 -10.9202425 -13.516270 -10.377952 -13.706729 -7.970190 -11.624714
> g5  0.2225315  1.331506  2.379584  2.996124  1.710600  1.058597
> g6 13.6685479 11.302242 12.325844 10.103907 10.001830 12.066131
>      [,73]      [,74]      [,75]      [,76]      [,77]      [,78]
> g1  3.58635809  5.690741  4.172261  5.387820  5.621021  5.394674
> g2 18.82645816 18.847631 18.629829 19.041418 17.659048 19.329822
> g3 -3.75584938 -1.655152 -1.811239 -4.112731 -4.263769 -5.582238
> g4 -11.47367684 -10.025294 -9.161142 -13.562384 -10.564153 -13.852200
> g5  0.01163896  3.577268  1.980380  1.032987  2.770731  1.533226
> g6 10.69955663 11.212962 12.269603 11.884114 10.636644 11.152263
>      [,79]      [,80]      [,81]      [,82]      [,83]      [,84]
> g1  4.4105779  4.6029323  4.56500496  4.367527  5.380164  5.4273765
> g2 19.1410904 15.7169809 17.53883594 17.419603 17.960849 18.3381625
> g3 -4.9166690 -0.6730186 -3.81234016 -4.264212 -6.271250 -4.0917934
> g4 -10.9541582 -10.6823470 -12.48190764 -12.755898 -10.219740 -11.0548885
> g5  0.8515518  1.0503681  0.02597338  2.699285  0.721474 -0.3265995
> g6 12.8161875  8.9421132 12.63085308 11.538503 11.722178  8.7453121
>      [,85]      [,86]      [,87]      [,88]      [,89]      [,90]

```

```

> g1 4.653092 4.744772 5.868073 6.560494 4.41374313 5.610824
> g2 17.109922 16.015486 19.842632 19.069869 17.93558000 18.103617
> g3 -2.571671 -5.659185 -4.608614 -4.458150 -4.10731537 -4.203695
> g4 -11.068923 -12.624786 -9.291319 -11.927320 -13.02321097 -12.811917
> g5 1.289552 2.282238 1.422763 1.622764 0.09502152 2.123966
> g6 9.337081 10.390021 11.648862 12.417930 12.86118757 11.585181
>      [,91]      [,92]      [,93]      [,94]      [,95]      [,96]
> g1 3.655231 5.92297709 5.594532 5.727926 3.839261 4.929862
> g2 17.851294 18.32045224 18.777437 20.073689 17.657657 16.148851
> g3 -3.380978 -5.53142388 -3.585946 -4.674287 -4.920095 -2.588720
> g4 -12.834692 -11.87266829 -12.290983 -11.395479 -12.027204 -13.453395
> g5 1.166630 0.03784201 1.726572 3.306152 1.073038 1.239465
> g6 10.954648 11.47770793 12.996580 8.922177 11.065604 11.828441
>      [,97]      [,98]      [,99]      [,100]
> g1 5.060089 2.481965 5.454253 5.0774444
> g2 19.692290 17.271134 15.537260 15.8655382
> g3 -4.892736 -4.263437 -3.641717 -3.9794759
> g4 -11.633394 -13.209137 -11.864635 -12.7489051
> g5 2.277451 1.169117 1.673870 -0.1733115
> g6 9.993153 10.906894 10.310814 10.5183231
head(data$Data$Y[[2]])
>      [,1]      [,2]      [,3]      [,4]      [,5]      [,6]
> g1 9.948509 14.1902215 9.472175410 13.525595 15.2023393 13.35551608
> g2 13.693329 14.5491579 12.236147973 13.832619 13.1579193 13.62498285
> g3 9.944288 10.8600114 9.853991067 9.957988 10.0641103 12.05572559
> g4 7.608072 14.0317228 10.999923388 12.418088 11.9441781 11.69112129
> g5 -1.001508 -1.6420794 -0.007065345 -2.260965 -1.2238051 -2.31613817
> g6 -1.504758 -0.7014416 -1.956536055 -2.055484 -0.2329952 0.06656525
>      [,7]      [,8]      [,9]      [,10]      [,11]      [,12]
> g1 12.9313841 15.920320 11.7873512 15.5284406 13.0943409 12.2718422
> g2 11.1914649 11.125735 12.5660697 12.7882782 11.0122571 10.2109819
> g3 11.8469884 9.919121 9.8297656 9.8182069 10.7495371 9.8810545
> g4 10.3481056 10.710947 10.3674912 12.1965693 10.6737369 8.6713656
> g5 -4.4396905 -1.397609 -1.9925676 -2.4034781 -3.2913450 0.2756007
> g6 -0.6787107 1.502859 -0.5370119 0.1933713 -0.7247887 -0.2251454
>      [,13]      [,14]      [,15]      [,16]      [,17]      [,18]
> g1 12.3012146 11.038065 12.847408 13.371809 13.7041637 14.5090985
> g2 10.2226867 10.562072 14.190406 9.303599 12.0570419 13.5412106
> g3 9.0253133 10.013826 12.926474 8.829644 10.0008158 9.9720776
> g4 12.6354302 10.859482 10.103639 10.648757 11.1163683 12.2015056
> g5 -0.7831814 -2.277604 -2.748106 -2.634764 -1.5775282 -3.1704298
> g6 -2.6685885 -1.469859 -1.149889 -2.490966 -0.9729241 -0.5301707
>      [,19]      [,20]      [,21]      [,22]      [,23]      [,24]
> g1 11.299426 14.0388550 14.1814221 12.8373883 9.508576 13.0064096
> g2 9.904300 11.7649206 12.7210911 12.3104639 11.122384 12.2937752
> g3 8.989161 9.9067289 11.0145523 10.8886026 8.869276 8.7895813
> g4 10.336963 9.9031883 11.4299294 11.0511164 9.582806 10.9271338
> g5 1.263874 -2.7823693 -0.5245449 0.5337292 -3.315519 -0.5860221
> g6 -3.774797 0.6910732 -1.9678048 -1.0686266 -2.635195 -1.2533016
>      [,25]      [,26]      [,27]      [,28]      [,29]      [,30]
> g1 10.732606 12.6257636 10.482928 14.1584787 12.6756832 12.942063
> g2 9.994278 10.5424698 11.205824 10.6823609 10.6087761 10.643474
> g3 10.091188 9.7648277 10.838791 12.0119327 8.9257628 9.751487

```

```

> g4 10.174802 12.0263061 10.885067 13.4689705 8.0596727 11.040014
> g5 -2.175861 0.4178679 -4.190449 -1.6150923 -1.7203607 -3.463298
> g6 -1.963736 -0.8426501 -2.763640 -0.8267138 0.7331591 -1.034681
>      [,31]      [,32]      [,33]      [,34]      [,35]      [,36]
> g1 13.2845847 13.2969523 11.9704449 13.369279 12.7079258 13.4308818
> g2 13.4648886 12.6173940 11.4121843 13.404501 12.3699831 9.6093653
> g3 9.8923785 10.9311813 6.9765048 10.064224 10.0328385 8.9825370
> g4 12.1910768 11.0352071 9.4160628 10.503397 9.1322501 12.1163873
> g5 0.6864578 -3.3087704 -0.9919851 -3.938833 -4.3531769 -3.5996567
> g6 -0.7689391 0.3169013 -2.9008971 -1.622064 0.4240979 -0.7543516
>      [,37]      [,38]      [,39]      [,40]      [,41]      [,42]      [,43]
> g1 12.507077 11.780734 11.3764345 10.0284497 10.936023 13.438335 13.432059
> g2 14.333239 12.664291 9.9126366 12.4797136 11.003269 10.968907 9.756589
> g3 8.949023 9.968663 8.7287935 9.8793372 8.845232 10.831307 10.777845
> g4 12.117538 10.549089 9.6959240 8.8876984 11.457789 10.752184 10.849595
> g5 -0.653499 -1.141197 -2.7429300 -1.9058742 -1.429589 -2.109230 -1.987744
> g6 -1.669149 -1.357247 -0.5948825 -0.4377632 -3.844224 0.307805 -1.156562
>      [,44]      [,45]      [,46]      [,47]      [,48]      [,49]
> g1 14.220396 11.045483 10.4525633 12.4112332 11.8731124 13.3532400
> g2 13.157719 12.828344 11.4686264 13.8241836 10.1705312 13.5762652
> g3 8.985435 9.848462 9.9677387 12.7576262 11.8557020 10.8245602
> g4 10.342474 12.260743 8.5028642 12.0841483 11.5928861 10.9836563
> g5 -1.487860 -1.264407 -1.8873743 -2.2295309 -1.8970537 -2.8578162
> g6 -2.222222 0.264414 -0.5428139 -0.1591217 -0.1606294 0.6430459
>      [,50]      [,51]      [,52]      [,53]      [,54]      [,55]
> g1 12.878322 14.3846207 12.3644766 14.147927 12.3457363 12.470742
> g2 12.178972 13.1115180 14.4696233 12.378412 12.9770893 10.896948
> g3 10.744376 9.7798237 9.0229090 7.825118 8.7442652 10.888025
> g4 12.749827 9.7352199 8.4573819 13.252391 10.8156762 12.273182
> g5 -4.005878 -3.1768597 0.5840697 -1.254032 -1.5058959 -2.952348
> g6 -1.943017 0.5986482 -1.0459673 -3.613648 0.6278244 -2.331696
>      [,56]      [,57]      [,58]      [,59]      [,60]      [,61]
> g1 12.4782356 12.1172123 8.966316505 15.5108387 13.6376266 11.712954
> g2 12.8799712 11.1404864 10.191240048 12.4722300 10.1997121 11.378397
> g3 9.8390599 7.7544058 11.061459459 9.9583801 8.7318671 11.928056
> g4 9.3944891 10.9329711 7.857285089 13.2266156 12.6685704 10.923103
> g5 -1.3457222 -0.3536978 -0.001519137 -0.8623282 -1.2889454 -3.129713
> g6 0.0114283 -1.0998112 0.948377955 -1.3272901 -0.7624468 -1.358733
>      [,62]      [,63]      [,64]      [,65]      [,66]      [,67]
> g1 13.22425865 11.2993027 12.659673 12.4085656 12.3136012 14.1980522
> g2 10.73681985 11.7450767 12.231193 9.9584254 12.8094149 11.4629312
> g3 9.86364146 8.9322345 10.061779 10.7777676 9.9694700 9.0368804
> g4 10.32836890 10.3686335 13.198781 10.9126091 12.0236106 12.5292635
> g5 -1.95088850 -1.8012877 -1.003361 0.1851967 -0.9115779 0.1860512
> g6 -0.07970153 -0.8638046 -1.179454 -0.5993835 0.3251259 -0.6014564
>      [,68]      [,69]      [,70]      [,71]      [,72]      [,73]
> g1 13.3793006 12.125547 13.78730556 9.279926 11.744737 13.2539050
> g2 13.3949805 10.215283 14.05463402 9.892414 13.237088 8.6832292
> g3 10.8611830 10.011459 8.05483582 10.923292 9.749937 8.9834724
> g4 11.4936919 9.969241 9.86681906 11.124393 9.245135 10.0255459
> g5 -1.8415196 -1.515651 -2.65865442 -3.085898 -0.706746 -1.9337640
> g6 0.2277101 0.177062 0.04502823 -3.122996 -1.600062 -0.3827523
>      [,74]      [,75]      [,76]      [,77]      [,78]      [,79]

```



```

> g1 11.572583 12.730862 14.340484 12.067477 11.8572852 13.4582834
> g2 12.712514 13.084804 11.524907 11.858854 13.2503385 11.1871683
> g3 9.794878 8.994664 12.908469 11.918010 9.8035252 9.0500562
> g4 8.513299 11.456633 12.051300 10.866142 9.1601472 10.8102503
> g5 -1.630638 1.569939 -2.869825 -1.935004 -0.7111727 -1.8325344
> g6 -1.312369 -0.425844 -2.616749 1.517214 1.0509228 -0.9054137
>      [,80]      [,81]      [,82]      [,83]      [,84]      [,85]
> g1 12.8498839 12.5063274 15.054707 12.129779 13.782206 13.324058
> g2 12.7685025 12.8957987 11.193109 9.623507 11.097235 12.917587
> g3 9.9681949 10.0209050 8.968449 10.013932 8.848713 8.938134
> g4 9.5474666 11.8346676 11.581142 8.843743 11.398186 9.310079
> g5 -1.6724099 -0.6148641 -2.122823 -2.055773 -1.837774 -1.744670
> g6 0.1874409 -0.5571816 -1.275753 1.251321 -1.461765 -1.143176
>      [,86]      [,87]      [,88]      [,89]      [,90]      [,91]
> g1 10.8390730 12.9895794 12.3372672 13.0832621 11.442714 10.3061903
> g2 11.2496059 13.4956601 11.5297350 11.6202721 12.131359 13.5203851
> g3 10.8617391 9.9955074 7.9554000 8.0269293 10.882742 8.8139988
> g4 9.8280857 11.0754789 10.4156703 10.2620039 9.568028 8.4451421
> g5 -0.4589174 0.3783464 -0.3750307 -1.1034548 -2.414278 -0.5185182
> g6 -1.9589648 -2.6470956 0.7584896 0.8978139 -1.176699 -0.5702781
>      [,92]      [,93]      [,94]      [,95]      [,96]      [,97]
> g1 11.266927 13.494598 14.277821 13.073171 11.8758586 13.5913022
> g2 12.771425 14.685187 12.491932 11.346665 11.4054797 10.4663578
> g3 8.908053 9.015920 8.860876 9.915142 8.7825983 11.0112119
> g4 11.995117 11.916406 13.801222 9.638339 10.1347857 12.0839281
> g5 -1.405765 1.190811 -1.278458 -3.343678 -3.0078396 0.5704218
> g6 -1.525401 0.341591 -1.418298 1.282014 -0.2044016 -1.8317988
>      [,98]      [,99]      [,100]
> g1 14.2708835 13.5897961 15.5494655
> g2 12.4372747 13.4138837 10.3536817
> g3 9.9621906 9.9454910 10.9312343
> g4 12.6380722 11.2432951 12.2587410
> g5 -0.3880157 -1.1474141 -0.9004263
> g6 -3.0175926 0.2285946 0.2263821

```

## 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      0      1      1      1      1      2      1      1      2      1      2      2      2
> rs2      2      1      0      2      0      2      0      1      0      2      2      2      2
> rs3      0      1      2      0      1      0      2      2      1      1      0      0      2
> rs4      0      1      1      1      2      2      1      0      1      0      0      1      1
> rs5      2      2      0      2      2      1      2      2      1      1      0      1      1
> rs6      2      1      1      1      1      1      1      1      1      2      1      0      1
>      [,14] [,15] [,16] [,17] [,18] [,19] [,20] [,21] [,22] [,23] [,24]
> rs1      1      2      2      0      1      1      0      1      2      2      0
> rs2      1      1      0      1      0      1      0      2      1      0      2
> rs3      1      2      1      0      0      1      2      1      2      0      1
> rs4      1      2      1      1      1      2      1      1      0      1      1
> rs5      1      0      1      0      0      1      1      1      2      0      1
> rs6      1      2      1      1      2      0      2      1      1      1      1
>      [,25] [,26] [,27] [,28] [,29] [,30] [,31] [,32] [,33] [,34] [,35]
> rs1      1      0      1      1      0      1      0      2      1      1      2

```



```

> rs2      0      0      2      1      1      1      0      1      1      2      1
> rs3      2      1      1      2      1      0      1      2      1      0      2
> rs4      1      1      1      1      1      2      1      1      0      1      0
> rs5      1      0      0      1      1      1      1      2      1      0      2
> rs6      1      1      1      0      2      0      1      2      1      0      1
>      [,36] [,37] [,38] [,39] [,40] [,41] [,42] [,43] [,44] [,45] [,46]
> rs1      1      1      2      2      2      0      1      1      1      1      1
> rs2      1      1      1      0      1      1      1      0      2      2      1
> rs3      0      1      2      2      2      0      1      1      0      0      2
> rs4      1      0      2      0      1      1      1      1      0      1      1
> rs5      0      2      0      2      1      1      1      0      2      1      2
> rs6      2      1      2      1      1      0      2      1      1      1      1
>      [,47] [,48] [,49] [,50] [,51] [,52] [,53] [,54] [,55] [,56] [,57]
> rs1      1      1      1      1      2      2      2      2      1      1      2
> rs2      2      1      2      1      0      2      2      2      0      1      0
> rs3      2      0      0      0      0      0      1      2      2      0      1
> rs4      1      1      1      0      2      0      2      2      1      2      2
> rs5      1      1      1      1      1      0      0      1      2      1      0
> rs6      0      1      2      2      2      0      1      1      1      1      0
>      [,58] [,59] [,60] [,61] [,62] [,63] [,64] [,65] [,66] [,67] [,68]
> rs1      1      2      2      2      1      1      1      0      1      1      1
> rs2      1      0      2      1      1      0      0      0      0      2      2
> rs3      2      1      1      1      0      1      2      1      1      1      1
> rs4      0      2      0      1      1      1      1      1      1      2      0
> rs5      1      1      1      1      1      2      1      0      1      0      2
> rs6      1      1      1      1      0      0      1      1      1      2      1
>      [,69] [,70] [,71] [,72] [,73] [,74] [,75] [,76] [,77] [,78] [,79]
> rs1      1      0      2      0      1      2      0      0      1      2      1
> rs2      2      1      2      1      1      1      1      1      1      2      2
> rs3      1      2      1      2      1      2      2      2      0      0      1
> rs4      2      0      2      1      1      1      2      0      2      1      1
> rs5      1      1      1      2      1      2      2      0      0      1      1
> rs6      2      0      2      1      1      2      2      1      1      1      1
>      [,80] [,81] [,82] [,83] [,84] [,85] [,86] [,87] [,88] [,89] [,90]
> rs1      1      1      0      1      1      1      1      1      2      1      2
> rs2      0      2      1      1      1      0      0      2      1      1      0
> rs3      2      1      1      0      1      2      0      1      1      1      2
> rs4      1      0      0      1      1      1      0      2      1      0      0
> rs5      0      1      1      1      0      1      1      1      1      1      1
> rs6      0      2      1      1      0      0      1      2      2      1      2
>      [,91] [,92] [,93] [,94] [,95] [,96] [,97] [,98] [,99] [,100]
> rs1      0      1      2      1      2      1      1      1      1      1
> rs2      2      0      2      2      0      0      2      1      0      1
> rs3      2      1      1      1      0      1      1      1      1      1
> rs4      1      2      1      2      0      0      1      1      2      1
> rs5      1      0      1      1      2      1      1      1      1      0
> rs6      2      1      2      0      1      2      1      1      1      0
head(data$Data$X[[2]] - 1)
>      [,1] [,2] [,3] [,4] [,5] [,6] [,7] [,8] [,9] [,10] [,11] [,12] [,13]
> rs1      1      1      0      1      1      1      1      2      1      2      2      0      1
> rs2      1      2      2      1      2      1      1      2      2      1      0      1      0
> rs3      2      1      2      1      2      2      2      1      0      1      2      2      0
> rs4      1      2      1      1      1      1      0      1      2      1      1      0      1

```

```

> rs5      1      1      1      1      1      0      0      2      0      1      0      1      1
> rs6      2      2      0      2      1      1      2      2      2      0      1      1      1
>      [,14] [,15] [,16] [,17] [,18] [,19] [,20] [,21] [,22] [,23] [,24]
> rs1      0      2      0      0      1      1      1      1      0      0      2
> rs2      1      2      0      1      2      0      1      1      2      2      1
> rs3      1      2      1      1      2      1      1      1      2      1      1
> rs4      1      1      0      1      2      0      1      1      2      1      1
> rs5      1      1      0      1      1      2      1      2      2      0      1
> rs6      0      1      0      1      1      0      1      0      1      1      1
>      [,25] [,26] [,27] [,28] [,29] [,30] [,31] [,32] [,33] [,34] [,35]
> rs1      0      1      1      1      2      1      2      2      2      2      2
> rs2      0      0      1      1      0      0      1      2      0      1      2
> rs3      1      1      2      2      1      2      1      2      0      0      0
> rs4      1      1      1      1      0      2      1      1      0      0      0
> rs5      2      2      0      0      1      0      2      1      2      0      0
> rs6      1      0      0      2      2      1      1      2      0      1      1
>      [,36] [,37] [,38] [,39] [,40] [,41] [,42] [,43] [,44] [,45] [,46]
> rs1      2      1      0      1      0      1      1      1      2      0      1
> rs2      1      2      1      0      1      1      0      0      1      1      1
> rs3      1      1      2      0      1      1      1      2      0      1      1
> rs4      2      2      1      1      0      2      2      1      1      2      0
> rs5      0      1      1      1      1      1      1      1      0      1      1
> rs6      2      0      1      1      2      0      2      0      1      1      1
>      [,47] [,48] [,49] [,50] [,51] [,52] [,53] [,54] [,55] [,56] [,57]
> rs1      1      1      1      0      1      1      1      2      1      1      1
> rs2      2      1      2      1      2      2      1      2      2      1      1
> rs3      2      1      2      1      2      0      0      0      1      0      0
> rs4      1      2      1      2      0      1      2      1      2      1      0
> rs5      2      2      0      0      0      1      0      2      1      1      0
> rs6      0      2      2      0      2      0      0      1      0      1      0
>      [,58] [,59] [,60] [,61] [,62] [,63] [,64] [,65] [,66] [,67] [,68]
> rs1      0      2      1      1      2      1      1      1      1      2      1
> rs2      2      2      0      1      0      1      1      0      2      1      2
> rs3      1      1      0      2      1      1      1      1      0      0      1
> rs4      0      1      2      2      0      2      1      1      1      1      1
> rs5      1      2      1      0      1      1      2      2      2      2      0
> rs6      1      0      1      1      2      0      1      2      2      2      1
>      [,69] [,70] [,71] [,72] [,73] [,74] [,75] [,76] [,77] [,78] [,79]
> rs1      0      1      0      1      1      1      0      1      1      1      1
> rs2      0      1      0      2      0      2      2      1      1      2      0
> rs3      1      0      1      0      1      1      1      2      2      1      1
> rs4      1      1      1      1      0      0      2      1      1      1      1
> rs5      1      1      1      1      2      0      2      1      1      1      1
> rs6      1      1      1      0      2      0      1      0      1      1      2
>      [,80] [,81] [,82] [,83] [,84] [,85] [,86] [,87] [,88] [,89] [,90]
> rs1      1      1      1      2      1      2      2      1      0      1      0
> rs2      1      2      0      1      1      1      2      1      2      2      1
> rs3      1      1      1      1      2      1      2      1      0      0      1
> rs4      0      2      1      1      2      1      1      0      1      1      1
> rs5      0      2      1      0      0      1      2      2      2      1      0
> rs6      1      1      1      2      1      0      0      0      1      2      1
>      [,91] [,92] [,93] [,94] [,95] [,96] [,97] [,98] [,99] [,100]
> rs1      1      0      2      1      1      1      2      2      1      2

```

```

> rs2      1      2      2      2      1      1      0      2      1      1
> rs3      1      1      1      1      1      1      2      1      1      1
> rs4      1      1      2      1      1      2      1      1      1      1
> rs5      2      0      2      1      0      1      2      2      1      1
> rs6      1      1      1      1      1      2      0      0      1      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  $\gamma$  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] 12.028811 11.919729 11.792414 11.644675 11.474381 11.279549 11.058506
> [8] 10.810038 10.533546 10.229192  9.898012  9.541965  9.163927  8.767605
> [15] 8.357401  7.938219  7.515262  7.093838  6.679184  6.276334  5.890012
> [22] 5.524560  5.183847  4.871179  4.589156  4.339539  4.123102  3.939537
> [29] 3.787457  3.664496  3.567537  3.493002  3.437166  3.396432  3.367533
> [36] 3.347651  3.334456  3.326095  3.321136  3.318506  3.317422  3.317322
> [43] 3.317816  3.318639  3.319614  3.320630  3.321620  3.322541  3.323374
> [50] 3.324116
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 initialization, and implement the `fssemR` algorithm, BIC is used to select optimal hyperparameters  $\lambda, \rho$ , 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$q, wt = TRUE)

> FSSEM@lambda = 194.256514, rho = 0.000000
> FSSEM@lambda = 194.256514, rho = 0.000000
> FSSEM@lambda = 194.256514, rho = 0.000000
> FSSEM@lambda = 194.256514, rho = 0.000000
> FSSEM@lambda = 194.256514, rho = 0.000000
> FSSEM@lambda = 194.256514, rho = 0.000000
> FSSEM@lambda = 194.256514, rho = 0.000000
> FSSEM@lambda = 194.256514, rho = 0.000000
> FSSEM@lambda = 194.256514, rho = 0.000000
> FSSEM@lambda = 90.165887, rho = 1.789177
> FSSEM@lambda = 90.165887, rho = 0.830462
> FSSEM@lambda = 90.165887, rho = 0.385466
> FSSEM@lambda = 90.165887, rho = 0.178918
> FSSEM@lambda = 90.165887, rho = 0.083046
> FSSEM@lambda = 90.165887, rho = 0.038547
> FSSEM@lambda = 90.165887, rho = 0.017892
> FSSEM@lambda = 90.165887, rho = 0.008305
> FSSEM@lambda = 90.165887, rho = 0.003855
> FSSEM@lambda = 90.165887, rho = 0.001789
> FSSEM@lambda = 41.851297, rho = 5.334570
> FSSEM@lambda = 41.851297, rho = 2.476088
> FSSEM@lambda = 41.851297, rho = 1.149298
> FSSEM@lambda = 41.851297, rho = 0.533457
> FSSEM@lambda = 41.851297, rho = 0.247609
> FSSEM@lambda = 41.851297, rho = 0.114930
> FSSEM@lambda = 41.851297, rho = 0.053346
> FSSEM@lambda = 41.851297, rho = 0.024761
> FSSEM@lambda = 41.851297, rho = 0.011493
> FSSEM@lambda = 41.851297, rho = 0.005335
> FSSEM@lambda = 19.425651, rho = 6.010180
> FSSEM@lambda = 19.425651, rho = 2.789679
> FSSEM@lambda = 19.425651, rho = 1.294854
> FSSEM@lambda = 19.425651, rho = 0.601018
> FSSEM@lambda = 19.425651, rho = 0.278968
> FSSEM@lambda = 19.425651, rho = 0.129485
> FSSEM@lambda = 19.425651, rho = 0.060102
> FSSEM@lambda = 19.425651, rho = 0.027897
> FSSEM@lambda = 19.425651, rho = 0.012949
> FSSEM@lambda = 19.425651, rho = 0.006010
> FSSEM@lambda = 9.016589, rho = 682.491856
> FSSEM@lambda = 9.016589, rho = 316.784658
> FSSEM@lambda = 9.016589, rho = 147.038413
> FSSEM@lambda = 9.016589, rho = 68.249186
> FSSEM@lambda = 9.016589, rho = 31.678466
```

```

> FSSEM@lambda = 9.016589, rho = 14.703841
> FSSEM@lambda = 9.016589, rho = 6.824919
> FSSEM@lambda = 9.016589, rho = 3.167847
> FSSEM@lambda = 9.016589, rho = 1.470384
> FSSEM@lambda = 9.016589, rho = 0.682492
> FSSEM@lambda = 4.185130, rho = 579.780365
> FSSEM@lambda = 4.185130, rho = 269.110207
> FSSEM@lambda = 4.185130, rho = 124.909893
> FSSEM@lambda = 4.185130, rho = 57.978036
> FSSEM@lambda = 4.185130, rho = 26.911021
> FSSEM@lambda = 4.185130, rho = 12.490989
> FSSEM@lambda = 4.185130, rho = 5.797804
> FSSEM@lambda = 4.185130, rho = 2.691102
> FSSEM@lambda = 4.185130, rho = 1.249099
> FSSEM@lambda = 4.185130, rho = 0.579780
> FSSEM@lambda = 1.942565, rho = 531.226478
> FSSEM@lambda = 1.942565, rho = 246.573489
> FSSEM@lambda = 1.942565, rho = 114.449275
> FSSEM@lambda = 1.942565, rho = 53.122648
> FSSEM@lambda = 1.942565, rho = 24.657349
> FSSEM@lambda = 1.942565, rho = 11.444928
> FSSEM@lambda = 1.942565, rho = 5.312265
> FSSEM@lambda = 1.942565, rho = 2.465735
> FSSEM@lambda = 1.942565, rho = 1.144493
> FSSEM@lambda = 1.942565, rho = 0.531226
> FSSEM@lambda = 0.901659, rho = 515.049664
> FSSEM@lambda = 0.901659, rho = 239.064877
> FSSEM@lambda = 0.901659, rho = 110.964086
> FSSEM@lambda = 0.901659, rho = 51.504966
> FSSEM@lambda = 0.901659, rho = 23.906488
> FSSEM@lambda = 0.901659, rho = 11.096409
> FSSEM@lambda = 0.901659, rho = 5.150497
> FSSEM@lambda = 0.901659, rho = 2.390649
> FSSEM@lambda = 0.901659, rho = 1.109641
> FSSEM@lambda = 0.901659, rho = 0.515050
> FSSEM@lambda = 0.418513, rho = 510.359917
> FSSEM@lambda = 0.418513, rho = 236.888089
> FSSEM@lambda = 0.418513, rho = 109.953711
> FSSEM@lambda = 0.418513, rho = 51.035992
> FSSEM@lambda = 0.418513, rho = 23.688809
> FSSEM@lambda = 0.418513, rho = 10.995371
> FSSEM@lambda = 0.418513, rho = 5.103599
> FSSEM@lambda = 0.418513, rho = 2.368881
> FSSEM@lambda = 0.418513, rho = 1.099537
> FSSEM@lambda = 0.418513, rho = 0.510360
> FSSEM@lambda = 0.194257, rho = 509.532862
> FSSEM@lambda = 0.194257, rho = 236.504204
> FSSEM@lambda = 0.194257, rho = 109.775527
> FSSEM@lambda = 0.194257, rho = 50.953286
> FSSEM@lambda = 0.194257, rho = 23.650420
> FSSEM@lambda = 0.194257, rho = 10.977553
> FSSEM@lambda = 0.194257, rho = 5.095329
> FSSEM@lambda = 0.194257, rho = 2.365042

```

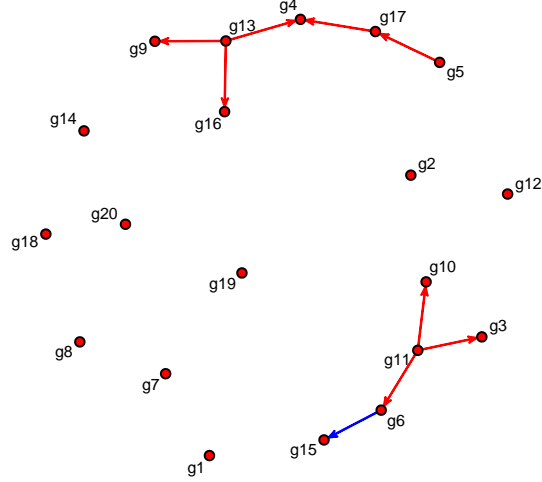


Figure 4: estimated differential GRN by fssemR

```
> FSSEM@lambda = 0.194257, rho = 1.097755
> FSSEM@lambda = 0.194257, rho = 0.509533

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
```

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`
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 = ecol)
```

Additionally, the differential 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)
rownames(diffGRN) = colnames(diffGRN) = rownames(data$Vars$B[[1]])
diffGRN
> 20 x 20 sparse Matrix of class "dgCMatrix"
> [[ suppressing 20 column names 'g1', 'g2', 'g3' ... ]]
>
> g1 . . . . . . 0 . . . . . . . .
> g2 . . . . . . 0 . 0 . . . . . .
> g3 . . . . . . . . -0.2187958 . . . .
> g4 0 . . . . . 0.0000000 . . . . . -0.2096113 . 0
> g5 . . . . . . . . . . . . . . . .
> g6 . . . . . . . . -0.3020784 . . 0 . .
> g7 . . . . . 0.0000000 . . . . . . . .
> g8 . . . . 0.0000000 . . . . . . . .
> g9 . . . . . . . . . . -0.2580067 . . .
> g10 . . . . . . . . -0.2433023 . . . .
> g11 . . . . . . . . . . . . . . . .
> g12 . . . . . . . . . . . . . . . .
> g13 . . . . 0.0000000 0.0000000 . . . . .
> g14 . . . . . . . . . . . . . . . .
> g15 . . . 0 . . . 0.2281523 . . . . . .
> g16 0 . . . . . . . . . . -0.3450633 . . .
> g17 . . . . -0.2116012 0.0000000 . . . . 0 . .
> g18 . . . . . . . . 0.0000000 . . . . .
> g19 0 . . . . . . . . . . . . . . . .
> g20 . . . . . . . . . . . . . . . .
>
> g1 . . . .
> g2 . . . .
> g3 . . . .
> g4 -0.1747657 0 . .
> g5 . . . 0 .
> g6 . . . .
> g7 . . . .
> g8 . . . .
> g9 . . . 0 .
> g10 . . . .
> g11 . . . .
> g12 0.0000000 . . .
> g13 . . . .
> g14 . . . .
> g15 0.0000000 . . .
> g16 . . . .
> g17 . . . .
> g18 . . . .
> g19 . . . .
> g20 . . . .
```

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=en_US.UTF-8
>  [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_0.1.5         RevoUtilsMath_10.0.0
>
> loaded via a namespace (and not attached):
>  [1] Rcpp_1.0.0          sna_2.4              compiler_3.4.0
>  [4] pillar_1.3.1        bindr_0.1.1          iterators_1.0.9
>  [7] tools_3.4.0         digest_0.6.18        memoise_1.1.0
> [10] evaluate_0.12       tibble_2.0.1         gtable_0.2.0
> [13] lattice_0.20-35     pkgconfig_2.0.2      rlang_0.3.1
> [16] foreach_1.4.4       igraph_1.2.2         rstudioapi_0.9.0
> [19] yaml_2.2.0          ggrepel_0.8.0        parallel_3.4.0
> [22] mvtnorm_1.0-8       xfun_0.4             bindrcpp_0.2.2
> [25] coda_0.19-2         knitr_1.21           withr_2.1.2
> [28] stringr_1.3.1       dplyr_0.7.8          devtools_1.12.0
> [31] RevoUtils_10.0.4    glmnet_2.0-16        grid_3.4.0
> [34] tidyselect_0.2.5    glue_1.3.0           R6_2.2.2
> [37] qtl_1.44-9          rmarkdown_1.11       purrr_0.3.0
> [40] magrittr_1.5        htmltools_0.3.6      scales_1.0.0.9000
> [43] codetools_0.2-15    MASS_7.3-49          assertthat_0.2.0
> [46] colorspace_1.4-0    stringi_1.2.4        lazyeval_0.2.1
> [49] munsell_0.5.0       statnet.common_4.1.4 crayon_1.3.4
```