ssemQr: Sparse Structural Equation Models based eQTL mapping

Xin Zhou

2020-04-22

In this vignette, we introduce the functionality of the `ssemQr` package to jointly implement eQTL-mapping and gene regulatory network (GRN) inference by gene expression and genetic perturbation data. To meet the space and time constraints in building this vignette within the `ssemQr` 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 `randomeQTLdata` in `ssemQr` to generate simulated data, and then apply Sparse Structural Equation Models based eQTL mapping (SSEMQ) to estimate the GRNs under two different conditions and their differential GRN. Also, please go to `https://github.com/Ivis4ml/ssemQr/tree/master/inst` for more large dataset analysis. In conlcusion, this vignette is composed by three sections as follow,

- Simulating GRN and it corresponding cis-eQTL effects, effects of trans-eQTLs are mediated via gene-gene interaction of GRN.
- Estimating GRNs and cis-eQTL effect from the simulated gene expression data and genetic perturbation data
- Visualization

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

Xin Zhou and Xiaodong Cai. Joint eQTL mapping and Inference of Gene Regulatory Network Improves Power of Detecting both cis- and trans-eQTLs, Bioinformatics, submitted.

Simulating GRN and it corresponding cis-eQTL effects (Acyclic example)

We are going to simulate a GRN and its corresponding gene expression and genetic perturbation data in the following steps:

1. Load the necessary packages

```
library(ssemQr)
library(network)
> network: Classes for Relational Data
> Version 1.16.0 created on 2019-11-30.
> 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(igraph)
>
> Attaching package: 'igraph'
> The following objects are masked from 'package:network':
```

```
>
>     %c%, %s%, add.edges, add.vertices, delete.edges, delete.vertices,
>     get.edge.attribute, get.edges, get.vertex.attribute, is.bipartite,
>     is.directed, list.edge.attributes, list.vertex.attributes,
>     set.edge.attribute, set.vertex.attribute
> The following objects are masked from 'package:stats':
>
>     decompose, spectrum
> The following object is masked from 'package:base':
>
>     union
library(Matrix)
```

2. Simulate 20 genes expression data with a sparse directed acyclic graph (DAG) GRN. Set *{cis}-eQTLs ratio as 10% of neighboring SNPs, and 5% genes have no {cis}-eQTLs*

```
N  = 100                                                                    # sample size
Ng = 20                                                                     # gene number
Nk = 20 * 3                                                                 # eQTL number
Ns = 15 / Ng                                                                # sparsity of GRN
sigma2 = 0.01                                                               # sigma2
Es = 0.1                                                                    # sparsity of {\it cis}-eQTL
set.seed(123)
data = randomeQTLdata(n = N, p = Ng, k = Nk, sparse =  Ns, sqtl = Es, intercept = 5, sigma2 = sigma2, es
```

Based on the mediation mechanism assumption, the eQTL-eGene associations are classified into two categories; cis-eQTLs and trans-eQTLs. The effects of trans-eQTLs are mediated by the GRN, which can be represented as series $\mathbf{BF}+\mathbf{B}^2\mathbf{F}+...+\mathbf{B}^n\mathbf{F}$. If $\rho(\mathbf{B}) \leq 1$, the effects of trans-eQTLs can be represented as $(\mathbf{I}-\mathbf{B})^{-1}\mathbf{F}-\mathbf{F}$.

```
Fw = (solve(diag(Ng) - data$Vars$B) %*% data$Vars$F)
Ftrans = sum(Fw[data$Vars$F == 0] != 0)
```

- Finally, 60 cis-eQTLs-eGene, 114 trans-eQTLs-eGene association simulated.
- Summary of GRN and QTLs

```
rownames(data$Vars$B) = colnames(data$Vars$B) = rownames(data$Vars$F) = rownames(data$Data$Y)
colnames(data$Vars$F) = rownames(data$Data$X)
GE = get.edgelist(graph.adjacency(t(data$Vars$B) != 0))
QE = which(t(data$Vars$F) != 0, arr.ind = TRUE)
QE[,2] = rownames(data$Vars$F)[QE[,2]]
QE[,1] = rownames(QE)
GRN = network(rbind(GE, QE), matrix.type = "edgelist", directed = TRUE)
plot(GRN, displaylabels = TRUE, label.cex = 0.5, vertex.col = rep(c(2, 5), times = c(length(unique(QE[,1
```

Implementing eQTL-mapping and GRN inference with simulated gene expression data and genetic perturbation data

1. Simulated gene expression

```
head(data$Data$Y)
>              [,1]       [,2]       [,3]       [,4]       [,5]        [,6]
> g_00001 -6.038139  0.6443969 -1.3587065  1.091444 -1.226743 -5.57685969
> g_00002 23.383864 14.2227603 14.3115817 14.989256 13.997098  5.21653112
> g_00003 12.965449  1.4776122  8.8602495  9.539895  5.740746 -0.56314204
> g_00004  8.680858 -0.3154836 12.2303879 11.590797 12.984470 -0.09114854
```

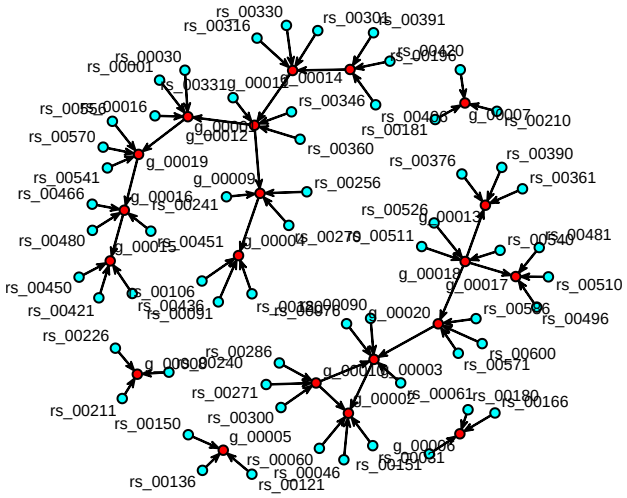

Figure 1: GRN QTL Network

```
> g_00005  6.166067 13.5259890 -0.3794916 14.182132 -1.131211 -1.69599359
> g_00006  1.529047 13.8584535 -2.1212353  9.248285 -2.687362  1.87320364
>               [,7]      [,8]       [,9]     [,10]     [,11]     [,12]
> g_00001 -5.3168539  2.917078 -11.060231  2.072620 -2.406864 -2.660673
> g_00002 11.0969931  7.098139   8.358089 13.075504  9.738768 21.622040
> g_00003 -2.0497066 -3.344469   1.235846 -9.349527  2.257174  4.014257
> g_00004  8.8091040  7.659602   9.481291  4.723875 10.662871  1.194306
> g_00005 -0.3431206  6.839499   6.222132  6.670297 13.504438  6.287138
> g_00006  2.0969778  5.489242   1.619971 13.962710  9.044138  1.762822
>              [,13]     [,14]     [,15]     [,16]     [,17]     [,18]     [,19]
> g_00001  0.7487899  1.709192  8.899143 -4.688677 -3.635110 -2.942381 -8.985299
> g_00002  1.1270648 13.813581 16.189511  6.612697 16.296739  8.057332  7.070144
> g_00003 -0.1060480 12.132866  5.869786 -3.944956  3.052335 -5.923862 -3.610565
> g_00004  8.8846909 17.339766  6.435624  1.199065  2.001491  4.167714 10.821980
> g_00005  6.1864841 11.685948  8.692697  8.589368  3.678769  8.617383  3.765058
> g_00006  9.8419935  2.368097 13.349509 -2.679751  1.746703  6.459423  1.672773
>              [,20]     [,21]      [,22]      [,23]      [,24]      [,25]
> g_00001 -11.0318016  2.845532 -0.2116834 -2.1680930 -2.9761235 -7.6594039
> g_00002   0.6870488 11.270394 11.4006258  7.1345237  6.3313823  3.7034281
> g_00003  -0.8711937  3.234500 10.1033906  1.4730168 -0.4842867 -1.8553575
> g_00004   6.6255378  7.569950  0.0305707  1.4260755 11.8862314  8.9440674
> g_00005   8.0242722  6.432018  8.7876071  0.5925095  6.2541864 -0.8474681
> g_00006   9.8121681  9.372386  1.5312734  1.7205105  1.8119920  1.4059919
>              [,26]      [,27]     [,28]      [,29]     [,30]     [,31]
> g_00001 -10.8600777 -0.6530769 -0.414423 -0.5156778  6.598562  3.114266
> g_00002  10.4724297 14.9394397 17.964168  4.3343203  7.673636 10.062633
> g_00003   3.0596264 10.7144885 -1.269667  0.8870281 -3.054480  1.931242
> g_00004   0.7561117  8.9586460  4.980906  1.1137763  5.882877 13.101000
> g_00005   9.3922373  5.6270000 -1.064443  5.6756813  6.109425  3.791205
> g_00006   5.9580352  5.7285995 -2.564782  4.9387256 10.022352  1.227683
>             [,32]      [,33]     [,34]     [,35]     [,36]      [,37]     [,38]
> g_00001 -6.471673  7.3144230 -6.646288 -4.816060  2.103165  6.7238047  4.203827
> g_00002  6.631378 -0.4353275  3.718508  9.953127 10.467397 10.4952372 13.883943
> g_00003  6.091258 -9.3621655 -6.519739  6.718040  2.565498 -0.2475049  7.121438
```

```
> g_00004  4.338571  2.8609885  8.757427 14.513295  8.692028 13.4417498 14.060510
> g_00005  6.188368 -1.1023432  6.052601  8.653607  8.081071  6.0791392  9.228961
> g_00006  9.382513 -2.0088045  9.399975 10.093147  9.257986  9.9098151 13.353713
>              [,39]     [,40]       [,41]      [,42]      [,43]     [,44]
> g_00001  -3.0060822 -1.134171 -12.6736888 -5.8349892 -1.8656431 -2.024858
> g_00002   0.1108343  9.061710   7.6852113 14.1420419  5.7148266 11.469324
> g_00003 -10.7957793  0.114919  -0.2166458  0.3976376 -4.9987882  8.874392
> g_00004   9.9425633  8.027816  10.4379657  7.8836556  0.5374723  7.193962
> g_00005   0.7059098  6.058761  -1.7728103 14.2017676  5.9692886 -1.930270
> g_00006   5.2615153  5.603717   4.8875901 10.1416156  5.1692746  4.855222
>            [,45]    [,46]     [,47]     [,48]      [,49]     [,50]      [,51]
> g_00001 -1.933522 3.867380 -1.925601 -2.226472  5.3090633  1.916836 -2.4231929
> g_00002 14.335534 7.587169 15.314490  8.195370 16.2872207  9.750388 10.9504148
> g_00003  0.604662 4.121844  2.117166  1.632544  0.9915105  2.751724  0.5667139
> g_00004  6.492399 9.981586  7.526914  1.554155  7.1437187 15.267246 10.2864788
> g_00005  1.298690 6.208491  1.418061  8.508896  3.7537718 -1.281104  9.3633607
> g_00006  5.648892 2.027159  1.435545  9.479543  1.7009150  1.663106  9.3399113
>             [,52]     [,53]      [,54]     [,55]     [,56]     [,57]     [,58]
> g_00001 -3.5473039 -4.393693  0.3921614  3.890589 -6.726872  5.942963 -1.053999
> g_00002 11.9620802 11.437627 11.1966680 10.351887 13.469142 16.155706 17.443236
> g_00003 -3.8307753  8.890505 -1.6812782  5.005066  4.777561  5.095566 15.108740
> g_00004 -0.3620542 12.871005  8.8236845 10.618419  6.444955 15.573605 12.087122
> g_00005 13.3969300  8.587354 14.1236456  6.266269  6.283303  3.813854  1.322333
> g_00006  6.3972207 -2.669502  9.4935484  5.512256  2.081688 -1.938316  5.738951
>             [,59]     [,60]     [,61]      [,62]     [,63]       [,64]
> g_00001 -11.195599 -5.768291  5.060398  8.7749914  4.056718 -11.7286004
> g_00002  -5.246004 11.652374  8.216822 16.4001093 15.751575   7.8079298
> g_00003  -4.083751  2.027858 -3.299455 -3.0149797  2.986897  -0.6390034
> g_00004  13.043358  6.707587  9.393615  4.5066203  9.444174  -3.0088597
> g_00005   3.259035 11.069753  1.240651 -0.3639891 -1.114934   7.8536911
> g_00006   1.992011  6.235394  6.058027  1.6109180  1.644187   5.5773164
>            [,65]     [,66]     [,67]       [,68]      [,69]      [,70]
> g_00001 -2.978133 -1.950763  4.502137   0.7128866 -1.7423517  0.6437823
> g_00002 14.146234 12.269135 13.572292  -2.7733150  0.7019292 14.1809632
> g_00003 -2.376841  3.047890  4.381545 -11.8750191 -9.5438658 -0.7949477
> g_00004  9.285481 13.710103  9.359436   2.3853670  9.9105672 15.1429150
> g_00005  6.109719  5.575372  6.161236   9.3143839  3.1989699 11.0601977
> g_00006  6.130370  5.667780  5.667409  10.0227647  5.4201123  1.9883107
>            [,71]      [,72]     [,73]       [,74]     [,75]     [,76]
> g_00001  3.204284   8.126654 -1.544988 -1.31803901 -1.433919  1.384086
> g_00002  2.631195   7.206733  6.423605 12.86863858  9.010747  7.645500
> g_00003 -6.985166 -11.300990 -5.791771  0.02377311 -4.602436 -8.878113
> g_00004  6.096830   1.121800 -4.578092  2.19404512  8.410683  7.535253
> g_00005  3.937240  -1.680335  5.628887  7.72330860  9.407079  6.069205
> g_00006  1.172539   9.417599 -2.518401  9.68875483  5.797374  9.848149
>            [,77]      [,78]     [,79]      [,80]     [,81]      [,82]
> g_00001 0.3878227  1.2264747  4.304476 -2.5372381 -1.112774  -7.923377
> g_00002 6.7227010  8.9927746 18.558877  9.2040634  7.421554  -5.127343
> g_00003 2.1070564 -8.6819711  4.701564 -0.3407032  3.681131 -14.115413
> g_00004 6.1500404 -0.7263027 13.323989  9.8980301 18.602395   5.700684
> g_00005 5.3864538  8.5552216  6.055221  8.6557686  9.357022   8.065133
> g_00006 9.8118246 10.2990689  8.943252 13.6588664  1.819483   5.856623
>            [,83]      [,84]     [,85]      [,86]      [,87]      [,88]
```

```
> g_00001 -4.249496 -0.4036571 -2.701486 -13.104847 -1.5264872 -7.6580429
> g_00002 10.003278  6.1962004  9.266007  14.269113 14.2560830 -0.5561409
> g_00003  3.918818 -0.7920674  3.193766  10.098628 -3.1187153 -4.9693846
> g_00004 11.438041  3.6336251  6.713172  -1.260435 -0.2156557  7.6892550
> g_00005  3.848850  2.9987655  4.584526  12.796822 -1.6794919 13.4044095
> g_00006  1.116631  4.7920443  1.116494   5.417585  1.6985779 10.2497881
>             [,89]     [,90]     [,91]     [,92]      [,93]      [,94]     [,95]
> g_00001 -1.615780 -5.119185  4.237222  2.229065 -0.2066921  2.0818405  1.716663
> g_00002 15.671043 11.592149  4.913900  8.238007 10.0928720 15.3091971 17.123965
> g_00003 -1.424904  1.213970 -1.772840 -7.786742 -0.2133384  0.4061676  6.721378
> g_00004  7.337562  6.691697  8.422380  7.081328  5.0635455  9.0410206  6.427174
> g_00005  6.115046 13.685374  3.914024 14.170359 -1.8505320 11.7049881 11.114235
> g_00006  5.659739 13.888826  5.589979  9.821148  1.5750276  5.6813180  5.707217
>              [,96]      [,97]     [,98]     [,99]    [,100]
> g_00001  0.8116527 -0.5738103  3.401589  4.173171  1.525293
> g_00002 13.5271154  9.3686685 18.328054 11.029991  5.203210
> g_00003  4.8479400 -1.5629534  5.037280  0.806792 -2.476404
> g_00004  7.6497027  7.8937133 10.206356 14.258247 11.295805
> g_00005 -1.8487619  8.0275200 11.730174  6.002121  7.047583
> g_00006  1.5968447 13.8801314  6.025969  1.343257  1.869980
```

2. Simulated eQTL's genotype

```
head(data$Data$X)
>          [,1] [,2] [,3] [,4] [,5] [,6] [,7] [,8] [,9] [,10] [,11] [,12] [,13]
> rs_00001    1    2    1    2    1    0    1    2    0     2     1     2     1
> rs_00002    1    2    1    2    1    0    0    2    0     1     1     2     0
> rs_00003    1    2    1    2    1    0    0    2    0     1     0     2     0
> rs_00004    1    2    1    2    1    0    0    2    0     1     0     2     1
> rs_00005    1    2    1    2    1    0    0    2    0     1     0     2     1
> rs_00006    1    2    2    2    1    0    0    2    0     1     0     2     1
>          [,14] [,15] [,16] [,17] [,18] [,19] [,20] [,21] [,22] [,23] [,24]
> rs_00001     1     2     1     0     1     0     1     1     2     0     1
> rs_00002     1     2     1     1     1     0     1     1     2     1     1
> rs_00003     1     2     1     1     1     0     1     1     2     1     1
> rs_00004     1     2     1     1     1     0     1     1     2     1     1
> rs_00005     1     2     1     1     1     0     1     1     2     1     1
> rs_00006     1     2     1     1     1     0     1     2     2     1     2
>          [,25] [,26] [,27] [,28] [,29] [,30] [,31] [,32] [,33] [,34] [,35]
> rs_00001     0     0     1     2     2     2     2     1     2     0     1
> rs_00002     0     0     1     1     1     2     2     1     2     0     1
> rs_00003     0     0     1     1     1     2     2     1     2     0     1
> rs_00004     0     0     0     1     1     2     2     1     2     0     1
> rs_00005     0     0     0     1     1     2     2     1     2     0     1
> rs_00006     0     0     0     1     1     2     2     1     2     0     1
>          [,36] [,37] [,38] [,39] [,40] [,41] [,42] [,43] [,44] [,45] [,46]
> rs_00001     1     2     2     1     1     0     1     1     1     1     1
> rs_00002     1     2     2     1     1     0     1     1     1     1     2
> rs_00003     1     2     2     1     1     0     1     2     1     1     2
> rs_00004     1     2     2     1     1     0     1     2     1     1     2
> rs_00005     1     2     2     1     1     0     1     2     1     1     2
> rs_00006     1     2     2     1     1     0     1     1     0     1     2
>          [,47] [,48] [,49] [,50] [,51] [,52] [,53] [,54] [,55] [,56] [,57]
> rs_00001     1     0     2     1     1     0     0     2     2     1     2
```

```
> rs_00002     1     0     2     1     1     0     0     2     2     1     2
> rs_00003     1     0     2     1     1     0     0     2     2     1     2
> rs_00004     1     0     2     1     1     0     0     2     2     1     2
> rs_00005     1     0     2     1     1     0     0     2     2     1     2
> rs_00006     1     0     2     1     1     0     0     2     2     1     2
>          [,58] [,59] [,60] [,61] [,62] [,63] [,64] [,65] [,66] [,67] [,68]
> rs_00001     1     0     0     2     2     2     1     1     0     2     1
> rs_00002     1     0     0     2     2     2     1     1     0     2     1
> rs_00003     0     0     0     2     1     2     1     1     0     2     1
> rs_00004     0     0     0     2     1     2     0     1     0     2     1
> rs_00005     0     0     0     2     1     2     0     1     0     2     2
> rs_00006     0     0     0     2     1     2     0     1     0     2     2
>          [,69] [,70] [,71] [,72] [,73] [,74] [,75] [,76] [,77] [,78] [,79]
> rs_00001     1     1     1     2     2     2     1     1     2     2     1
> rs_00002     1     1     1     2     2     2     1     1     2     2     1
> rs_00003     1     1     1     2     2     2     1     1     2     2     1
> rs_00004     1     1     1     2     2     2     1     1     2     1     1
> rs_00005     1     1     1     2     2     2     1     1     2     1     1
> rs_00006     1     1     1     2     2     2     1     1     2     1     1
>          [,80] [,81] [,82] [,83] [,84] [,85] [,86] [,87] [,88] [,89] [,90]
> rs_00001     2     2     0     1     2     0     0     0     1     1     1
> rs_00002     1     2     0     1     2     0     0     0     1     1     1
> rs_00003     1     2     0     1     2     0     0     1     1     1     1
> rs_00004     1     2     0     1     2     0     0     2     0     2     1
> rs_00005     1     2     0     1     2     1     0     2     0     2     1
> rs_00006     1     2     0     1     2     1     0     2     0     2     1
>          [,91] [,92] [,93] [,94] [,95] [,96] [,97] [,98] [,99] [,100]
> rs_00001     2     1     1     1     0     0     0     0     1      2
> rs_00002     1     1     1     1     0     0     0     0     1      2
> rs_00003     1     1     1     1     0     0     0     0     1      2
> rs_00004     1     1     1     1     0     0     0     0     1      1
> rs_00005     1     2     1     1     0     0     0     0     1      1
> rs_00006     1     2     1     1     0     0     0     0     1      1
```

3. `data$Data$Sk` stores each genes' nearby SNPs' indices, which is the candidate pool of cis-eQTL mapping filtered by distance constraint

```
head(data$Data$Sk)
> [[1]]
>  [1]  1  2  3  4  5  6  7  8  9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
> [26] 26 27 28 29 30
>
> [[2]]
>  [1] 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55
> [26] 56 57 58 59 60
>
> [[3]]
>  [1] 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85
> [26] 86 87 88 89 90
>
> [[4]]
>  [1]  91  92  93  94  95  96  97  98  99 100 101 102 103 104 105 106 107 108 109
> [20] 110 111 112 113 114 115 116 117 118 119 120
>
```

```
> [[5]]
>  [1] 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139
> [20] 140 141 142 143 144 145 146 147 148 149 150
>
> [[6]]
>  [1] 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169
> [20] 170 171 172 173 174 175 176 177 178 179 180
```

Initialization of ssemQr by ridge regression

We implement our ssemQr 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 10-fold cross-validation.

```
X     = data$Data$X
Y     = data$Data$Y
Sk    = data$Data$Sk
gamma = cv.ridgeRegression(X, Y, Sk, ngamma = 10, nfold = 10, data$Vars$n, data$Vars$p, data$Vars$q)
>   [1] 6.3522569 5.5227972 4.0958865 3.2110817 2.7474365 2.5828221 2.7211478
>   [8] 2.9769015 3.1492752 3.2105083 5.7272243 5.0210032 3.6719598 2.7018944
>  [15] 2.1070388 1.7704783 1.7814009 1.9559592 2.0864278 2.1340119 5.4678958
>  [22] 4.8710421 3.6079306 2.5510549 1.8257179 1.2503900 0.9952741 0.9987344
>  [29] 1.0577530 1.0845648 5.5440533 4.9976447 3.7695414 2.6425265 1.8496802
>  [36] 1.1585370 0.7021353 0.5110323 0.4918077 0.5002854 5.6419720 5.1101398
>  [43] 3.8880463 2.7263598 1.9061438 1.1825437 0.6673229 0.3835734 0.3035372
>  [50] 0.2981736 5.6761598 5.1476984 3.9263664 2.7547164 1.9271808 1.1965676
>  [57] 0.6710365 0.3720622 0.2783720 0.2693739 5.6844648 5.1567396 3.9355293
>  [64] 2.7615720 1.9323839 1.2003088 0.6729144 0.3720001 0.2769582 0.2676446
>  [71] 5.6863030 5.1587372 3.9375507 2.7630881 1.9335405 1.2011542 0.6733817
>  [78] 0.3721399 0.2769240 0.2676184 5.6867013 5.1591697 3.9379883 2.7634166
>  [85] 1.9337912 1.2013378 0.6734843 0.3721751 0.2769236 0.2676269 5.6867872
>  [92] 5.1592630 3.9380827 2.7634874 1.9338454 1.2013773 0.6735065 0.3721844
>  [99] 0.2769253 0.2675866
fit0   = ridgeRegression(X, Y, Sk, gamma[1], gamma[2], data$Vars$n, data$Vars$p, data$Vars$q, trans = F
```

Run ssemQr algorithm for data

Then, we chose the `fit0` object from ridge regression as intialization, and implement the `ssemQr` 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.SSEMiPALM(X = X, Y = Y, B = fit0$B, F = fit0$F, Sk = Sk, sigma2 = fit0$sigma2,
                       nlambda = 10, nrho = 10, p = data$Vars$p, wt = TRUE)
> SSEM@lambda = 111.536547, rho = 74.290336
> SSEM@lambda = 51.770679, rho = 74.290336
> SSEM@lambda = 24.029821, rho = 74.290336
> SSEM@lambda = 11.153655, rho = 74.290336
> SSEM@lambda = 5.177068, rho = 74.290336
> SSEM@lambda = 2.402982, rho = 74.290336
> SSEM@lambda = 1.115365, rho = 74.290336
> SSEM@lambda = 0.517707, rho = 74.290336
> SSEM@lambda = 0.240298, rho = 74.290336
> SSEM@lambda = 0.111537, rho = 74.290336
```

```
> SSEM@lambda = 267.267555, rho = 34.482519
> SSEM@lambda = 124.054610, rho = 34.482519
> SSEM@lambda = 57.581049, rho = 34.482519
> SSEM@lambda = 26.726756, rho = 34.482519
> SSEM@lambda = 12.405461, rho = 34.482519
> SSEM@lambda = 5.758105, rho = 34.482519
> SSEM@lambda = 2.672676, rho = 34.482519
> SSEM@lambda = 1.240546, rho = 34.482519
> SSEM@lambda = 0.575810, rho = 34.482519
> SSEM@lambda = 0.267268, rho = 34.482519
> SSEM@lambda = 361.595415, rho = 16.005368
> SSEM@lambda = 167.837724, rho = 16.005368
> SSEM@lambda = 77.903371, rho = 16.005368
> SSEM@lambda = 36.159541, rho = 16.005368
> SSEM@lambda = 16.783772, rho = 16.005368
> SSEM@lambda = 7.790337, rho = 16.005368
> SSEM@lambda = 3.615954, rho = 16.005368
> SSEM@lambda = 1.678377, rho = 16.005368
> SSEM@lambda = 0.779034, rho = 16.005368
> SSEM@lambda = 0.361595, rho = 16.005368
> SSEM@lambda = 383.983710, rho = 7.429034
> SSEM@lambda = 178.229450, rho = 7.429034
> SSEM@lambda = 82.726783, rho = 7.429034
> SSEM@lambda = 38.398371, rho = 7.429034
> SSEM@lambda = 17.822945, rho = 7.429034
> SSEM@lambda = 8.272678, rho = 7.429034
> SSEM@lambda = 3.839837, rho = 7.429034
> SSEM@lambda = 1.782295, rho = 7.429034
> SSEM@lambda = 0.827268, rho = 7.429034
> SSEM@lambda = 0.383984, rho = 7.429034
> SSEM@lambda = 391.092890, rho = 3.448252
> SSEM@lambda = 181.529239, rho = 3.448252
> SSEM@lambda = 84.258409, rho = 3.448252
> SSEM@lambda = 39.109289, rho = 3.448252
> SSEM@lambda = 18.152924, rho = 3.448252
> SSEM@lambda = 8.425841, rho = 3.448252
> SSEM@lambda = 3.910929, rho = 3.448252
> SSEM@lambda = 1.815292, rho = 3.448252
> SSEM@lambda = 0.842584, rho = 3.448252
> SSEM@lambda = 0.391093, rho = 3.448252
> SSEM@lambda = 391.536481, rho = 1.600537
> SSEM@lambda = 181.735136, rho = 1.600537
> SSEM@lambda = 84.353978, rho = 1.600537
> SSEM@lambda = 39.153648, rho = 1.600537
> SSEM@lambda = 18.173514, rho = 1.600537
> SSEM@lambda = 8.435398, rho = 1.600537
> SSEM@lambda = 3.915365, rho = 1.600537
> SSEM@lambda = 1.817351, rho = 1.600537
> SSEM@lambda = 0.843540, rho = 1.600537
> SSEM@lambda = 0.391536, rho = 1.600537
> SSEM@lambda = 381.269630, rho = 0.742903
> SSEM@lambda = 176.969686, rho = 0.742903
> SSEM@lambda = 82.142052, rho = 0.742903
```

```
> SSEM@lambda = 38.126963, rho = 0.742903
> SSEM@lambda = 17.696969, rho = 0.742903
> SSEM@lambda = 8.214205, rho = 0.742903
> SSEM@lambda = 3.812696, rho = 0.742903
> SSEM@lambda = 1.769697, rho = 0.742903
> SSEM@lambda = 0.821421, rho = 0.742903
> SSEM@lambda = 0.381270, rho = 0.742903
> SSEM@lambda = 375.191741, rho = 0.344825
> SSEM@lambda = 174.148579, rho = 0.344825
> SSEM@lambda = 80.832610, rho = 0.344825
> SSEM@lambda = 37.519174, rho = 0.344825
> SSEM@lambda = 17.414858, rho = 0.344825
> SSEM@lambda = 8.083261, rho = 0.344825
> SSEM@lambda = 3.751917, rho = 0.344825
> SSEM@lambda = 1.741486, rho = 0.344825
> SSEM@lambda = 0.808326, rho = 0.344825
> SSEM@lambda = 0.375192, rho = 0.344825
> SSEM@lambda = 381.235153, rho = 0.160054
> SSEM@lambda = 176.953683, rho = 0.160054
> SSEM@lambda = 82.134624, rho = 0.160054
> SSEM@lambda = 38.123515, rho = 0.160054
> SSEM@lambda = 17.695368, rho = 0.160054
> SSEM@lambda = 8.213462, rho = 0.160054
> SSEM@lambda = 3.812352, rho = 0.160054
> SSEM@lambda = 1.769537, rho = 0.160054
> SSEM@lambda = 0.821346, rho = 0.160054
> SSEM@lambda = 0.381235, rho = 0.160054
> SSEM@lambda = 390.821386, rho = 0.074290
> SSEM@lambda = 181.403218, rho = 0.074290
> SSEM@lambda = 84.199915, rho = 0.074290
> SSEM@lambda = 39.082139, rho = 0.074290
> SSEM@lambda = 18.140322, rho = 0.074290
> SSEM@lambda = 8.419992, rho = 0.074290
> SSEM@lambda = 3.908214, rho = 0.074290
> SSEM@lambda = 1.814032, rho = 0.074290
> SSEM@lambda = 0.841999, rho = 0.074290
> SSEM@lambda = 0.390821, rho = 0.074290
fitQtl = SSEMiPALM(X = X, Y = Y, B = fit0$B, F = fit0$F, Sk = Sk, sigma2 = fit0$sigma2,
                   lambda = fitOpt$lambda, rho = fitOpt$rho,
                   Wb = 1 / abs(fit0$B), Wf = 1 / abs(fit0$F),
                   p = data$Vars$p, maxit = 1000, trans = TRUE, strict = TRUE)
> SSEMQ     niter = 1,  relerr = 0.953770,  logLik = 5634.438145
> SSEMQ     niter = 2,  relerr = 0.354811,  logLik = 4463.149911
> SSEMQ     niter = 3,  relerr = 0.142849,  logLik = 3087.634889
> SSEMQ     niter = 4,  relerr = 0.057526,  logLik = 2537.623961
> SSEMQ     niter = 5,  relerr = 0.021952,  logLik = 2444.238039
> SSEMQ     niter = 6,  relerr = 0.008531,  logLik = 2271.852885
> SSEMQ     niter = 7,  relerr = 0.009151,  logLik = 2044.442995
> SSEMQ     niter = 8,  relerr = 0.009271,  logLik = 1849.003795
> SSEMQ     niter = 9,  relerr = 0.007953,  logLik = 1718.129885
> SSEMQ     niter = 10,     relerr = 0.006245,  logLik = 1637.257199
> SSEMQ     niter = 11,     relerr = 0.004701,  logLik = 1580.825947
> SSEMQ     niter = 12,     relerr = 0.003572,  logLik = 1534.437267
```

```
> SSEMQ     niter = 13,     relerr = 0.003015,  logLik = 1492.497339
> SSEMQ     niter = 14,     relerr = 0.002892,  logLik = 1455.922198
> SSEMQ     niter = 15,     relerr = 0.002848,  logLik = 1424.261764
> SSEMQ     niter = 16,     relerr = 0.002734,  logLik = 1397.537206
> SSEMQ     niter = 17,     relerr = 0.002538,  logLik = 1378.020813
> SSEMQ     niter = 18,     relerr = 0.002326,  logLik = 1362.211957
> SSEMQ     niter = 19,     relerr = 0.002105,  logLik = 1348.954560
> SSEMQ     niter = 20,     relerr = 0.001847,  logLik = 1339.347527
> SSEMQ     niter = 21,     relerr = 0.001616,  logLik = 1332.638455
> SSEMQ     niter = 22,     relerr = 0.001444,  logLik = 1325.999281
> SSEMQ     niter = 23,     relerr = 0.001290,  logLik = 1320.347520
> SSEMQ     niter = 24,     relerr = 0.001178,  logLik = 1315.849093
> SSEMQ     niter = 25,     relerr = 0.001111,  logLik = 1311.488999
> SSEMQ     niter = 26,     relerr = 0.001072,  logLik = 1306.993141
> SSEMQ     niter = 27,     relerr = 0.001023,  logLik = 1302.647502
> SSEMQ     niter = 28,     relerr = 0.000913,  logLik = 1302.319618
> SSEMQ     niter = 29,     relerr = 0.000826,  logLik = 1301.507024
> SSEMQ     niter = 30,     relerr = 0.000748,  logLik = 1300.791071
> SSEMQ     niter = 31,     relerr = 0.000664,  logLik = 1300.083465
> SSEMQ     niter = 32,     relerr = 0.000602,  logLik = 1299.495115
> SSEMQ     niter = 33,     relerr = 0.000523,  logLik = 1299.044852
> SSEMQ     niter = 34,     relerr = 0.000473,  logLik = 1298.681270
> SSEMQ     niter = 35,     relerr = 0.000440,  logLik = 1298.235535
> SSEMQ     niter = 36,     relerr = 0.000417,  logLik = 1297.777575
> SSEMQ     niter = 37,     relerr = 0.000400,  logLik = 1297.342376
> SSEMQ     niter = 38,     relerr = 0.000387,  logLik = 1296.919559
> SSEMQ     niter = 39,     relerr = 0.000377,  logLik = 1296.494972
> SSEMQ     niter = 40,     relerr = 0.000358,  logLik = 1296.173563
> SSEMQ     niter = 41,     relerr = 0.000342,  logLik = 1295.909269
> SSEMQ     niter = 42,     relerr = 0.000329,  logLik = 1295.662175
> SSEMQ     niter = 43,     relerr = 0.000317,  logLik = 1295.421919
> SSEMQ     niter = 44,     relerr = 0.000306,  logLik = 1295.190474
> SSEMQ     niter = 45,     relerr = 0.000296,  logLik = 1294.979195
> SSEMQ     niter = 46,     relerr = 0.000285,  logLik = 1294.802668
> SSEMQ     niter = 47,     relerr = 0.000272,  logLik = 1294.672330
> SSEMQ     niter = 48,     relerr = 0.000257,  logLik = 1294.592153
> SSEMQ     niter = 49,     relerr = 0.000239,  logLik = 1294.557456
> SSEMQ     niter = 50,     relerr = 0.000220,  logLik = 1294.556603
> SSEMQ     niter = 51,     relerr = 0.000199,  logLik = 1294.574490
> SSEMQ     niter = 52,     relerr = 0.000180,  logLik = 1294.596334
> SSEMQ     niter = 53,     relerr = 0.000162,  logLik = 1294.610736
> SSEMQ     niter = 54,     relerr = 0.000147,  logLik = 1294.611150
> SSEMQ     niter = 55,     relerr = 0.000137,  logLik = 1294.595798
> SSEMQ     niter = 56,     relerr = 0.000129,  logLik = 1294.566508
> SSEMQ     niter = 57,     relerr = 0.000125,  logLik = 1294.526996
> SSEMQ     niter = 58,     relerr = 0.000122,  logLik = 1294.481324
> SSEMQ     niter = 59,     relerr = 0.000121,  logLik = 1294.432906
> SSEMQ     niter = 60,     relerr = 0.000121,  logLik = 1294.384148
> SSEMQ     niter = 61,     relerr = 0.000120,  logLik = 1294.336603
> SSEMQ     niter = 62,     relerr = 0.000120,  logLik = 1294.291378
> SSEMQ     niter = 63,     relerr = 0.000120,  logLik = 1294.249508
> SSEMQ     niter = 64,     relerr = 0.000119,  logLik = 1294.212128
> SSEMQ     niter = 65,     relerr = 0.000117,  logLik = 1294.180393
```

```
> SSEMQ     niter = 66,     relerr = 0.000115,  logLik = 1294.155203
> SSEMQ     niter = 67,     relerr = 0.000111,  logLik = 1294.136893
> SSEMQ     niter = 68,     relerr = 0.000107,  logLik = 1294.125021
> SSEMQ     niter = 69,     relerr = 0.000101,  logLik = 1294.118347
> SSEMQ     niter = 70,     relerr = 0.000095,  logLik = 1294.115034
> SSEMQ     niter = 71,     relerr = 0.000089,  logLik = 1294.113003
> SSEMQ     niter = 72,     relerr = 0.000083,  logLik = 1294.110342
> SSEMQ     niter = 73,     relerr = 0.000079,  logLik = 1294.105667
> SSEMQ     niter = 74,     relerr = 0.000076,  logLik = 1294.098335
> SSEMQ     niter = 75,     relerr = 0.000074,  logLik = 1294.088475
> SSEMQ     niter = 76,     relerr = 0.000073,  logLik = 1294.076855
> SSEMQ     niter = 77,     relerr = 0.000073,  logLik = 1294.064630
> SSEMQ     niter = 78,     relerr = 0.000072,  logLik = 1294.053049
> SSEMQ     niter = 79,     relerr = 0.000072,  logLik = 1294.043188
> SSEMQ     niter = 80,     relerr = 0.000070,  logLik = 1294.035766
> SSEMQ     niter = 81,     relerr = 0.000068,  logLik = 1294.031065
> SSEMQ     niter = 82,     relerr = 0.000065,  logLik = 1294.028943
> SSEMQ     niter = 83,     relerr = 0.000061,  logLik = 1294.028925
> SSEMQ     niter = 84,     relerr = 0.000057,  logLik = 1294.030338
> SSEMQ     niter = 85,     relerr = 0.000053,  logLik = 1294.032438
> SSEMQ     niter = 86,     relerr = 0.000049,  logLik = 1294.034533
> SSEMQ     niter = 87,     relerr = 0.000045,  logLik = 1294.036065
> SSEMQ     niter = 88,     relerr = 0.000042,  logLik = 1294.036659
> SSEMQ     niter = 89,     relerr = 0.000040,  logLik = 1294.036132
> SSEMQ     niter = 90,     relerr = 0.000038,  logLik = 1294.034489
> SSEMQ     niter = 91,     relerr = 0.000038,  logLik = 1294.031884
> SSEMQ     niter = 92,     relerr = 0.000038,  logLik = 1294.028584
> SSEMQ     niter = 93,     relerr = 0.000038,  logLik = 1294.024919
> SSEMQ     niter = 94,     relerr = 0.000038,  logLik = 1294.021237
> SSEMQ     niter = 95,     relerr = 0.000039,  logLik = 1294.017854
> SSEMQ     niter = 96,     relerr = 0.000038,  logLik = 1294.015022
> SSEMQ     niter = 97,     relerr = 0.000038,  logLik = 1294.012895
> SSEMQ     niter = 98,     relerr = 0.000037,  logLik = 1294.011514
> SSEMQ     niter = 99,     relerr = 0.000035,  logLik = 1294.010815
> SSEMQ     niter = 100,    relerr = 0.000033,  logLik = 1294.010638
> SSEMQ     niter = 101,    relerr = 0.000031,  logLik = 1294.010760
> SSEMQ     niter = 102,    relerr = 0.000029,  logLik = 1294.010930
> SSEMQ     niter = 103,    relerr = 0.000027,  logLik = 1294.010910
> SSEMQ     niter = 104,    relerr = 0.000025,  logLik = 1294.010511
> SSEMQ     niter = 105,    relerr = 0.000024,  logLik = 1294.009615
> SSEMQ     niter = 106,    relerr = 0.000023,  logLik = 1294.008186
> SSEMQ     niter = 107,    relerr = 0.000024,  logLik = 1294.006267
> SSEMQ     niter = 108,    relerr = 0.000024,  logLik = 1294.003969
> SSEMQ     niter = 109,    relerr = 0.000025,  logLik = 1294.001445
> SSEMQ     niter = 110,    relerr = 0.000026,  logLik = 1293.998871
> SSEMQ     niter = 111,    relerr = 0.000026,  logLik = 1293.996413
> SSEMQ     niter = 112,    relerr = 0.000027,  logLik = 1293.994209
> SSEMQ     niter = 113,    relerr = 0.000027,  logLik = 1293.992355
> SSEMQ     niter = 114,    relerr = 0.000026,  logLik = 1293.990896
> SSEMQ     niter = 115,    relerr = 0.000026,  logLik = 1293.989823
> SSEMQ     niter = 116,    relerr = 0.000025,  logLik = 1293.989085
> SSEMQ     niter = 117,    relerr = 0.000023,  logLik = 1293.988596
> SSEMQ     niter = 118,    relerr = 0.000022,  logLik = 1293.988254
```

```
> SSEMQ     niter = 119,    relerr = 0.000021,  logLik = 1293.987952
> SSEMQ     niter = 120,    relerr = 0.000019,  logLik = 1293.987592
> SSEMQ     niter = 121,    relerr = 0.000018,  logLik = 1293.987101
> SSEMQ     niter = 122,    relerr = 0.000017,  logLik = 1293.986435
> SSEMQ     niter = 123,    relerr = 0.000017,  logLik = 1293.985582
> SSEMQ     niter = 124,    relerr = 0.000017,  logLik = 1293.984560
> SSEMQ     niter = 125,    relerr = 0.000018,  logLik = 1293.983416
> SSEMQ     niter = 126,    relerr = 0.000018,  logLik = 1293.982213
> SSEMQ     niter = 127,    relerr = 0.000019,  logLik = 1293.981020
> SSEMQ     niter = 128,    relerr = 0.000019,  logLik = 1293.979907
> SSEMQ     niter = 129,    relerr = 0.000020,  logLik = 1293.978931
> SSEMQ     niter = 130,    relerr = 0.000020,  logLik = 1293.978136
> SSEMQ     niter = 131,    relerr = 0.000020,  logLik = 1293.977540
> SSEMQ     niter = 132,    relerr = 0.000019,  logLik = 1293.977143
> SSEMQ     niter = 133,    relerr = 0.000019,  logLik = 1293.976927
> SSEMQ     niter = 134,    relerr = 0.000018,  logLik = 1293.976856
> SSEMQ     niter = 135,    relerr = 0.000017,  logLik = 1293.976891
> SSEMQ     niter = 136,    relerr = 0.000016,  logLik = 1293.976986
> SSEMQ     niter = 137,    relerr = 0.000015,  logLik = 1293.977102
> SSEMQ     niter = 138,    relerr = 0.000014,  logLik = 1293.977205
> SSEMQ     niter = 139,    relerr = 0.000014,  logLik = 1293.977276
> SSEMQ     niter = 140,    relerr = 0.000013,  logLik = 1293.977307
> SSEMQ     niter = 141,    relerr = 0.000013,  logLik = 1293.977301
> SSEMQ     niter = 142,    relerr = 0.000013,  logLik = 1293.977271
> SSEMQ     niter = 143,    relerr = 0.000013,  logLik = 1293.977236
> SSEMQ     niter = 144,    relerr = 0.000013,  logLik = 1293.977218
> SSEMQ     niter = 145,    relerr = 0.000013,  logLik = 1293.977236
> SSEMQ     niter = 146,    relerr = 0.000012,  logLik = 1293.977307
> SSEMQ     niter = 147,    relerr = 0.000012,  logLik = 1293.977438
> SSEMQ     niter = 148,    relerr = 0.000012,  logLik = 1293.977631
> SSEMQ     niter = 149,    relerr = 0.000011,  logLik = 1293.977879
> SSEMQ     niter = 150,    relerr = 0.000011,  logLik = 1293.978169
> SSEMQ     niter = 151,    relerr = 0.000010,  logLik = 1293.978484
> SSEMQ     niter = 152,    relerr = 0.000009,  logLik = 1293.978804
> SSEMQ     niter = 153,    relerr = 0.000009,  logLik = 1293.979108
> SSEMQ     niter = 154,    relerr = 0.000008,  logLik = 1293.979381
> SSEMQ     niter = 155,    relerr = 0.000008,  logLik = 1293.979609
> SSEMQ     niter = 156,    relerr = 0.000007,  logLik = 1293.979784
> SSEMQ     niter = 157,    relerr = 0.000007,  logLik = 1293.979905
> SSEMQ     niter = 158,    relerr = 0.000007,  logLik = 1293.979973
> SSEMQ     niter = 159,    relerr = 0.000007,  logLik = 1293.979997
> SSEMQ     niter = 160,    relerr = 0.000007,  logLik = 1293.979985
> SSEMQ     niter = 161,    relerr = 0.000008,  logLik = 1293.979947
> SSEMQ     niter = 162,    relerr = 0.000008,  logLik = 1293.979895
> SSEMQ     niter = 163,    relerr = 0.000008,  logLik = 1293.979837
> SSEMQ     niter = 164,    relerr = 0.000008,  logLik = 1293.979776
> SSEMQ     niter = 165,    relerr = 0.000007,  logLik = 1293.979716
> SSEMQ     niter = 166,    relerr = 0.000007,  logLik = 1293.979653
> SSEMQ     niter = 167,    relerr = 0.000007,  logLik = 1293.979585
> SSEMQ     niter = 168,    relerr = 0.000007,  logLik = 1293.979504
> SSEMQ     niter = 169,    relerr = 0.000006,  logLik = 1293.979404
> SSEMQ     niter = 170,    relerr = 0.000006,  logLik = 1293.979277
> SSEMQ     niter = 171,    relerr = 0.000005,  logLik = 1293.979117
```

```
> SSEMQ     niter = 172,    relerr = 0.000005,  logLik = 1293.978921
> SSEMQ     niter = 173,    relerr = 0.000005,  logLik = 1293.978688
> SSEMQ     niter = 174,    relerr = 0.000005,  logLik = 1293.978419
> SSEMQ     niter = 175,    relerr = 0.000005,  logLik = 1293.978119
> SSEMQ     niter = 176,    relerr = 0.000005,  logLik = 1293.977792
> SSEMQ     niter = 177,    relerr = 0.000005,  logLik = 1293.977448
> SSEMQ     niter = 178,    relerr = 0.000006,  logLik = 1293.977093
> SSEMQ     niter = 179,    relerr = 0.000006,  logLik = 1293.976736
> SSEMQ     niter = 180,    relerr = 0.000006,  logLik = 1293.976383
> SSEMQ     niter = 181,    relerr = 0.000006,  logLik = 1293.976039
> SSEMQ     niter = 182,    relerr = 0.000006,  logLik = 1293.975708
> SSEMQ     niter = 183,    relerr = 0.000006,  logLik = 1293.975393
> SSEMQ     niter = 184,    relerr = 0.000006,  logLik = 1293.975092
> SSEMQ     niter = 185,    relerr = 0.000006,  logLik = 1293.974806
> SSEMQ     niter = 186,    relerr = 0.000006,  logLik = 1293.974531
> SSEMQ     niter = 187,    relerr = 0.000006,  logLik = 1293.974267
> SSEMQ     niter = 188,    relerr = 0.000006,  logLik = 1293.974009
> SSEMQ     niter = 189,    relerr = 0.000006,  logLik = 1293.973757
> SSEMQ     niter = 190,    relerr = 0.000006,  logLik = 1293.973509
> SSEMQ     niter = 191,    relerr = 0.000006,  logLik = 1293.973264
> SSEMQ     niter = 192,    relerr = 0.000006,  logLik = 1293.973023
> SSEMQ     niter = 193,    relerr = 0.000006,  logLik = 1293.972787
> SSEMQ     niter = 194,    relerr = 0.000006,  logLik = 1293.972559
> SSEMQ     niter = 195,    relerr = 0.000006,  logLik = 1293.972340
> SSEMQ     niter = 196,    relerr = 0.000006,  logLik = 1293.972133
> SSEMQ     niter = 197,    relerr = 0.000006,  logLik = 1293.971940
> SSEMQ     niter = 198,    relerr = 0.000006,  logLik = 1293.971763
> SSEMQ     niter = 199,    relerr = 0.000006,  logLik = 1293.971604
> SSEMQ     niter = 200,    relerr = 0.000006,  logLik = 1293.971463
> SSEMQ     niter = 201,    relerr = 0.000006,  logLik = 1293.971341
> SSEMQ     niter = 202,    relerr = 0.000006,  logLik = 1293.971237
> SSEMQ     niter = 203,    relerr = 0.000006,  logLik = 1293.971151
> SSEMQ     niter = 204,    relerr = 0.000006,  logLik = 1293.971080
> SSEMQ     niter = 205,    relerr = 0.000006,  logLik = 1293.971025
> SSEMQ     niter = 206,    relerr = 0.000006,  logLik = 1293.970984
> SSEMQ     niter = 207,    relerr = 0.000006,  logLik = 1293.970954
> SSEMQ     niter = 208,    relerr = 0.000005,  logLik = 1293.970936
> SSEMQ     niter = 209,    relerr = 0.000005,  logLik = 1293.970927
> SSEMQ     niter = 210,    relerr = 0.000005,  logLik = 1293.970928
> SSEMQ     niter = 211,    relerr = 0.000005,  logLik = 1293.970938
> SSEMQ     niter = 212,    relerr = 0.000005,  logLik = 1293.970956
> SSEMQ     niter = 213,    relerr = 0.000005,  logLik = 1293.970982
> SSEMQ     niter = 214,    relerr = 0.000005,  logLik = 1293.971014
> SSEMQ     niter = 215,    relerr = 0.000005,  logLik = 1293.971054
> SSEMQ     niter = 216,    relerr = 0.000004,  logLik = 1293.971101
> SSEMQ     niter = 217,    relerr = 0.000004,  logLik = 1293.971154
> SSEMQ     niter = 218,    relerr = 0.000004,  logLik = 1293.971212
> SSEMQ     niter = 219,    relerr = 0.000004,  logLik = 1293.971275
> SSEMQ     niter = 220,    relerr = 0.000004,  logLik = 1293.971343
> SSEMQ     niter = 221,    relerr = 0.000004,  logLik = 1293.971415
> SSEMQ     niter = 222,    relerr = 0.000004,  logLik = 1293.971489
> SSEMQ     niter = 223,    relerr = 0.000004,  logLik = 1293.971567
> SSEMQ     niter = 224,    relerr = 0.000004,  logLik = 1293.971647
```

```
> SSEMQ     niter = 225,    relerr = 0.000003,  logLik = 1293.971728
> SSEMQ     niter = 226,    relerr = 0.000003,  logLik = 1293.971811
> SSEMQ     niter = 227,    relerr = 0.000003,  logLik = 1293.971895
> SSEMQ     niter = 228,    relerr = 0.000003,  logLik = 1293.971979
> SSEMQ     niter = 229,    relerr = 0.000003,  logLik = 1293.972064
> SSEMQ     niter = 230,    relerr = 0.000003,  logLik = 1293.972148
> SSEMQ     niter = 231,    relerr = 0.000003,  logLik = 1293.972230
> SSEMQ     niter = 232,    relerr = 0.000003,  logLik = 1293.972312
> SSEMQ     niter = 233,    relerr = 0.000003,  logLik = 1293.972391
> SSEMQ     niter = 234,    relerr = 0.000003,  logLik = 1293.972467
> SSEMQ     niter = 235,    relerr = 0.000003,  logLik = 1293.972539
> SSEMQ     niter = 236,    relerr = 0.000002,  logLik = 1293.972608
> SSEMQ     niter = 237,    relerr = 0.000002,  logLik = 1293.972672
> SSEMQ     niter = 238,    relerr = 0.000002,  logLik = 1293.972731
> SSEMQ     niter = 239,    relerr = 0.000002,  logLik = 1293.972786
> SSEMQ     niter = 240,    relerr = 0.000002,  logLik = 1293.972835
> SSEMQ     niter = 241,    relerr = 0.000002,  logLik = 1293.972879
> SSEMQ     niter = 242,    relerr = 0.000002,  logLik = 1293.972919
> SSEMQ     niter = 243,    relerr = 0.000002,  logLik = 1293.972953
> SSEMQ     niter = 244,    relerr = 0.000002,  logLik = 1293.972983
> SSEMQ     niter = 245,    relerr = 0.000002,  logLik = 1293.973008
> SSEMQ     niter = 246,    relerr = 0.000002,  logLik = 1293.973029
> SSEMQ     niter = 247,    relerr = 0.000002,  logLik = 1293.973046
> SSEMQ     niter = 248,    relerr = 0.000002,  logLik = 1293.973059
> SSEMQ     niter = 249,    relerr = 0.000002,  logLik = 1293.973068
> SSEMQ     niter = 250,    relerr = 0.000002,  logLik = 1293.973072
> SSEMQ     niter = 251,    relerr = 0.000002,  logLik = 1293.973073
> SSEMQ     niter = 252,    relerr = 0.000002,  logLik = 1293.973069
> SSEMQ     niter = 253,    relerr = 0.000002,  logLik = 1293.973061
> SSEMQ     niter = 254,    relerr = 0.000002,  logLik = 1293.973049
> SSEMQ     niter = 255,    relerr = 0.000002,  logLik = 1293.973032
> SSEMQ     niter = 256,    relerr = 0.000002,  logLik = 1293.973011
> SSEMQ     niter = 257,    relerr = 0.000002,  logLik = 1293.972986
> SSEMQ     niter = 258,    relerr = 0.000002,  logLik = 1293.972957
> SSEMQ     niter = 259,    relerr = 0.000002,  logLik = 1293.972924
> SSEMQ     niter = 260,    relerr = 0.000002,  logLik = 1293.972887
> SSEMQ     niter = 261,    relerr = 0.000002,  logLik = 1293.972848
> SSEMQ     niter = 262,    relerr = 0.000002,  logLik = 1293.972806
> SSEMQ     niter = 263,    relerr = 0.000002,  logLik = 1293.972761
> SSEMQ     niter = 264,    relerr = 0.000002,  logLik = 1293.972714
> SSEMQ     niter = 265,    relerr = 0.000002,  logLik = 1293.972665
> SSEMQ     niter = 266,    relerr = 0.000002,  logLik = 1293.972615
> SSEMQ     niter = 267,    relerr = 0.000002,  logLik = 1293.972564
> SSEMQ     niter = 268,    relerr = 0.000002,  logLik = 1293.972512
> SSEMQ     niter = 269,    relerr = 0.000002,  logLik = 1293.972459
> SSEMQ     niter = 270,    relerr = 0.000002,  logLik = 1293.972406
> SSEMQ     niter = 271,    relerr = 0.000002,  logLik = 1293.972352
> SSEMQ     niter = 272,    relerr = 0.000002,  logLik = 1293.972297
> SSEMQ     niter = 273,    relerr = 0.000002,  logLik = 1293.972242
> SSEMQ     niter = 274,    relerr = 0.000002,  logLik = 1293.972187
> SSEMQ     niter = 275,    relerr = 0.000002,  logLik = 1293.972132
> SSEMQ     niter = 276,    relerr = 0.000002,  logLik = 1293.972077
> SSEMQ     niter = 277,    relerr = 0.000002,  logLik = 1293.972021
```

```
> SSEMQ     niter = 278,    relerr = 0.000002,  logLik = 1293.971966
> SSEMQ     niter = 279,    relerr = 0.000002,  logLik = 1293.971911
> SSEMQ     niter = 280,    relerr = 0.000002,  logLik = 1293.971856
> SSEMQ     niter = 281,    relerr = 0.000002,  logLik = 1293.971802
> SSEMQ     niter = 282,    relerr = 0.000002,  logLik = 1293.971748
> SSEMQ     niter = 283,    relerr = 0.000002,  logLik = 1293.971695
> SSEMQ     niter = 284,    relerr = 0.000002,  logLik = 1293.971643
> SSEMQ     niter = 285,    relerr = 0.000002,  logLik = 1293.971591
> SSEMQ     niter = 286,    relerr = 0.000002,  logLik = 1293.971541
> SSEMQ     niter = 287,    relerr = 0.000002,  logLik = 1293.971492
> SSEMQ     niter = 288,    relerr = 0.000002,  logLik = 1293.971445
> SSEMQ     niter = 289,    relerr = 0.000002,  logLik = 1293.971398
> SSEMQ     niter = 290,    relerr = 0.000002,  logLik = 1293.971353
> SSEMQ     niter = 291,    relerr = 0.000002,  logLik = 1293.971309
> SSEMQ     niter = 292,    relerr = 0.000002,  logLik = 1293.971266
> SSEMQ     niter = 293,    relerr = 0.000002,  logLik = 1293.971225
> SSEMQ     niter = 294,    relerr = 0.000002,  logLik = 1293.971185
> SSEMQ     niter = 295,    relerr = 0.000002,  logLik = 1293.971147
> SSEMQ     niter = 296,    relerr = 0.000002,  logLik = 1293.971110
> SSEMQ     niter = 297,    relerr = 0.000002,  logLik = 1293.971074
> SSEMQ     niter = 298,    relerr = 0.000002,  logLik = 1293.971040
> SSEMQ     niter = 299,    relerr = 0.000002,  logLik = 1293.971007
> SSEMQ     niter = 300,    relerr = 0.000002,  logLik = 1293.970976
> SSEMQ     niter = 301,    relerr = 0.000002,  logLik = 1293.970946
> SSEMQ     niter = 302,    relerr = 0.000002,  logLik = 1293.970917
> SSEMQ     niter = 303,    relerr = 0.000002,  logLik = 1293.970889
> SSEMQ     niter = 304,    relerr = 0.000002,  logLik = 1293.970863
> SSEMQ     niter = 305,    relerr = 0.000002,  logLik = 1293.970838
> SSEMQ     niter = 306,    relerr = 0.000002,  logLik = 1293.970814
> SSEMQ     niter = 307,    relerr = 0.000002,  logLik = 1293.970792
> SSEMQ     niter = 308,    relerr = 0.000002,  logLik = 1293.970770
> SSEMQ     niter = 309,    relerr = 0.000002,  logLik = 1293.970750
> SSEMQ     niter = 310,    relerr = 0.000002,  logLik = 1293.970732
> SSEMQ     niter = 311,    relerr = 0.000002,  logLik = 1293.970714
> SSEMQ     niter = 312,    relerr = 0.000002,  logLik = 1293.970697
> SSEMQ     niter = 313,    relerr = 0.000002,  logLik = 1293.970682
> SSEMQ     niter = 314,    relerr = 0.000002,  logLik = 1293.970668
> SSEMQ     niter = 315,    relerr = 0.000002,  logLik = 1293.970654
> SSEMQ     niter = 316,    relerr = 0.000002,  logLik = 1293.970642
> SSEMQ     niter = 317,    relerr = 0.000002,  logLik = 1293.970631
> SSEMQ     niter = 318,    relerr = 0.000002,  logLik = 1293.970621
> SSEMQ     niter = 319,    relerr = 0.000002,  logLik = 1293.970612
> SSEMQ     niter = 320,    relerr = 0.000002,  logLik = 1293.970604
> SSEMQ     niter = 321,    relerr = 0.000002,  logLik = 1293.970596
> SSEMQ     niter = 322,    relerr = 0.000002,  logLik = 1293.970589
> SSEMQ     niter = 323,    relerr = 0.000002,  logLik = 1293.970584
> SSEMQ     niter = 324,    relerr = 0.000002,  logLik = 1293.970578
> SSEMQ     niter = 325,    relerr = 0.000002,  logLik = 1293.970574
> SSEMQ     niter = 326,    relerr = 0.000002,  logLik = 1293.970570
> SSEMQ     niter = 327,    relerr = 0.000001,  logLik = 1293.970567
> SSEMQ     niter = 328,    relerr = 0.000001,  logLik = 1293.970564
> SSEMQ     niter = 329,    relerr = 0.000001,  logLik = 1293.970562
> SSEMQ     niter = 330,    relerr = 0.000001,  logLik = 1293.970560
```

```
> SSEMQ     niter = 331,    relerr = 0.000001,  logLik = 1293.970559
> SSEMQ     niter = 332,    relerr = 0.000001,  logLik = 1293.970559
> SSEMQ     niter = 333,    relerr = 0.000001,  logLik = 1293.970559
> SSEMQ     niter = 334,    relerr = 0.000001,  logLik = 1293.970559
> SSEMQ     niter = 335,    relerr = 0.000001,  logLik = 1293.970560
> SSEMQ     niter = 336,    relerr = 0.000001,  logLik = 1293.970561
> SSEMQ     niter = 337,    relerr = 0.000001,  logLik = 1293.970563
> SSEMQ     niter = 338,    relerr = 0.000001,  logLik = 1293.970565
> SSEMQ     niter = 339,    relerr = 0.000001,  logLik = 1293.970567
> SSEMQ     niter = 340,    relerr = 0.000001,  logLik = 1293.970570
> SSEMQ     niter = 341,    relerr = 0.000001,  logLik = 1293.970573
> SSEMQ     niter = 342,    relerr = 0.000001,  logLik = 1293.970576
> SSEMQ     niter = 343,    relerr = 0.000001,  logLik = 1293.970579
> SSEMQ     niter = 344,    relerr = 0.000001,  logLik = 1293.970582
> SSEMQ     niter = 345,    relerr = 0.000001,  logLik = 1293.970586
> SSEMQ     niter = 346,    relerr = 0.000001,  logLik = 1293.970589
> SSEMQ     niter = 347,    relerr = 0.000001,  logLik = 1293.970593
> SSEMQ     niter = 348,    relerr = 0.000001,  logLik = 1293.970597
> SSEMQ     niter = 349,    relerr = 0.000001,  logLik = 1293.970601
> SSEMQ     niter = 350,    relerr = 0.000001,  logLik = 1293.970604
> SSEMQ     niter = 351,    relerr = 0.000001,  logLik = 1293.970608
> SSEMQ     niter = 352,    relerr = 0.000001,  logLik = 1293.970612
> SSEMQ     niter = 353,    relerr = 0.000001,  logLik = 1293.970615
> SSEMQ     niter = 354,    relerr = 0.000001,  logLik = 1293.970619
> SSEMQ     niter = 355,    relerr = 0.000001,  logLik = 1293.970622
> SSEMQ     niter = 356,    relerr = 0.000001,  logLik = 1293.970626
> SSEMQ     niter = 357,    relerr = 0.000001,  logLik = 1293.970629
> SSEMQ     niter = 358,    relerr = 0.000001,  logLik = 1293.970632
> SSEMQ     niter = 359,    relerr = 0.000001,  logLik = 1293.970636
> SSEMQ     niter = 360,    relerr = 0.000001,  logLik = 1293.970639
> SSEMQ     niter = 361,    relerr = 0.000001,  logLik = 1293.970642
> SSEMQ     niter = 362,    relerr = 0.000001,  logLik = 1293.970644
> SSEMQ     niter = 363,    relerr = 0.000001,  logLik = 1293.970647
> SSEMQ     niter = 364,    relerr = 0.000001,  logLik = 1293.970650
> SSEMQ     niter = 365,    relerr = 0.000001,  logLik = 1293.970652
> SSEMQ     niter = 366,    relerr = 0.000001,  logLik = 1293.970654
> SSEMQ     niter = 367,    relerr = 0.000001,  logLik = 1293.970656
> SSEMQ     niter = 368,    relerr = 0.000001,  logLik = 1293.970658
> SSEMQ     niter = 369,    relerr = 0.000001,  logLik = 1293.970659
```

Comparing our estimated cis-QTL and GRN with ground truth

```
cat("Power of estimated GRN = ", fssemR:::TPR(fitQtl$B, data$Vars$B))
> Power of estimated GRN =  1
cat("FDR of estimated GRN = ", fssemR:::FDR(fitQtl$B, data$Vars$B))
> FDR of estimated GRN =  0
cat("Power of estimated cis-eQTL =", fssemR:::TPR(fitQtl$F, data$Vars$F))
> Power of estimated cis-eQTL = 1
cat("FDR of estimated cis-eQTL =", fssemR:::FDR(fitQtl$F, data$Vars$F))
> FDR of estimated cis-eQTL = 0
```

Based on these 4 metrics, we can get the performance of `ssemQr` in cis-eQTL indentification and GRN

estimation.

Comparing estimated trans-eQTL

```
Ftrans = (solve(diag(Ng) - fitQtl$B) %*% fitQtl$F)
Ftrue = (solve(diag(Ng) - data$Vars$B) %*% data$Vars$F)
PRcurve = calcPR(Ftrans, Ftrue)[-1,]
ggplot(PRcurve, aes(x = recall, y = precision)) + geom_point(size = 0.5) + geom_path() + labs(x ="Recall
```

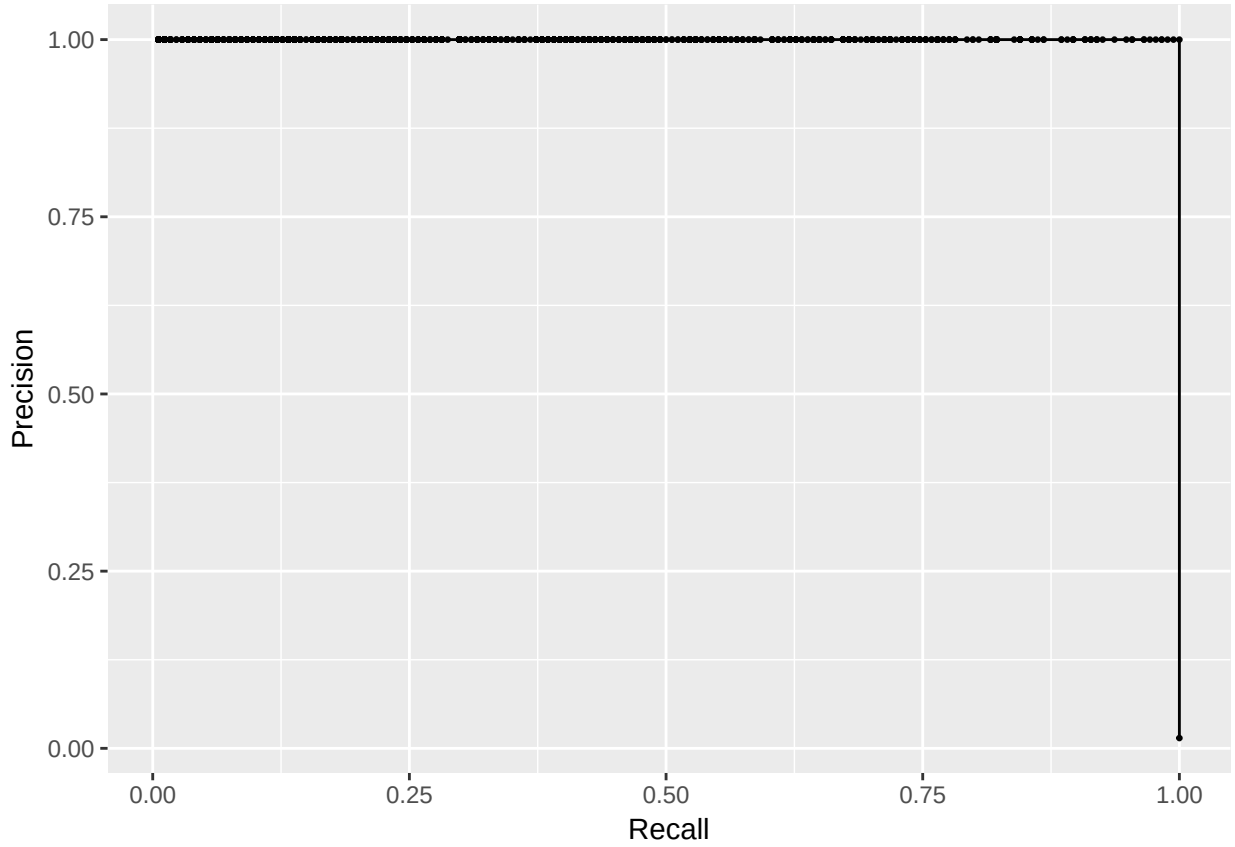

Figure 2: PR curve of trans-eQTL

Estimated GRN and eQTL visualization

```
rownames(fitQtl$B) = colnames(fitQtl$B) = rownames(fitQtl$F) = rownames(data$Data$Y)
colnames(fitQtl$F) = rownames(data$Data$X)
GE = get.edgelist(graph.adjacency(t(fitQtl$B) != 0))
QE = which(t(fitQtl$F) != 0, arr.ind = TRUE)
QE[,2] = rownames(fitQtl$F)[QE[,2]]
QE[,1] = rownames(QE)
GRN = network(rbind(GE, QE), matrix.type = "edgelist", directed = TRUE)
plot(GRN, displaylabels = TRUE, label.cex = 0.5, vertex.col = rep(c(2, 5), times = c(length(unique(QE[,1
```

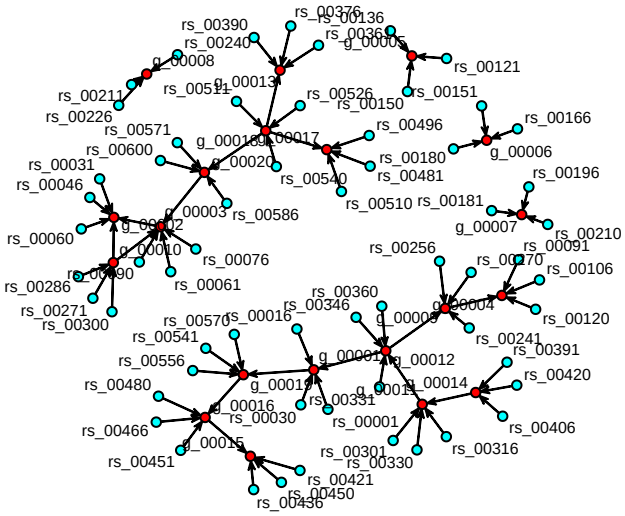

Figure 3: GRN QTL Network

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        igraph_1.2.2         ggnetwork_0.5.1
> [4] ggplot2_2.2.1        network_1.16.0       ssemQr_0.1.0
> [7] RevoUtilsMath_10.0.0
>
> loaded via a namespace (and not attached):
>  [1] Rcpp_1.0.3           sna_2.5              RSpectra_0.16-0
>  [4] plyr_1.8.5           compiler_3.4.0       pillar_1.4.3.9001
>  [7] iterators_1.0.9      tools_3.4.0          digest_0.6.23
> [10] evaluate_0.14        tibble_3.0.1.9000    lifecycle_0.2.0.9000
> [13] gtable_0.3.0         lattice_0.20-35      pkgconfig_2.0.3
> [16] rlang_0.4.5.9000     foreach_1.4.4        ggrepel_0.8.1
```

```
> [19] yaml_2.2.1           parallel_3.4.0       mvtnorm_1.0-8
> [22] xfun_0.12            coda_0.19-3          fssemR_0.1.6
> [25] stringr_1.4.0        knitr_1.28           RevoUtils_10.0.4
> [28] vctrs_0.2.99.9011    stabs_0.6-3          glmnet_2.0-8
> [31] grid_3.4.0           R6_2.4.1             rARPACK_0.11-0
> [34] qtl_1.45-11          rmarkdown_2.1        farver_2.0.3.9000
> [37] magrittr_1.5         scales_1.1.0.9000    codetools_0.2-15
> [40] htmltools_0.4.0      ellipsis_0.3.0.9000  MASS_7.3-49
> [43] colorspace_1.4-1     labeling_0.3         stringi_1.4.5
> [46] lazyeval_0.2.2       munsell_0.5.0        statnet.common_4.1.4
> [49] crayon_1.3.4
```