ssemQr: Sparse Structural Equation Models based eQTL mapping

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2020-02-18

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. Identification of trans-eQTLs via Joint eQTL mapping and inference of Gene Regultory Network 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, e
```

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[,2
```

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
```

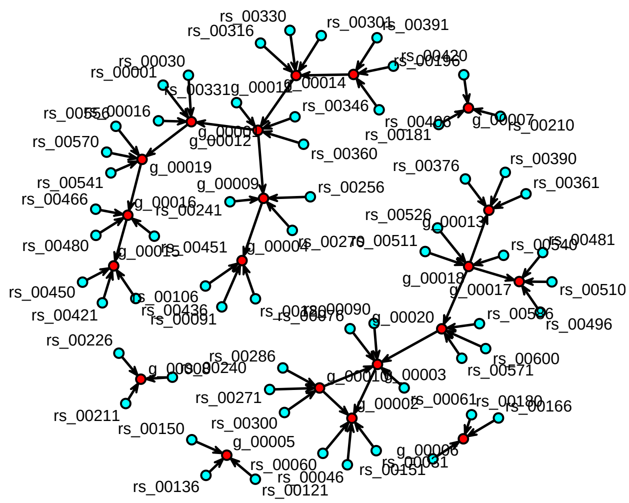

Figure 1: GRN QTL Network

```
> 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 = 66.864403, rho = 74.290336
> SSEM@lambda = 40.084157, rho = 74.290336
> SSEM@lambda = 24.029821, rho = 74.290336
> SSEM@lambda = 14.405499, rho = 74.290336
> SSEM@lambda = 8.635870, rho = 74.290336
> SSEM@lambda = 5.177068, rho = 74.290336
> SSEM@lambda = 3.103571, rho = 74.290336
> SSEM@lambda = 1.860542, rho = 74.290336
> SSEM@lambda = 1.115365, rho = 74.290336
```

```
> SSEM@lambda = 177.166051, rho = 44.535886
> SSEM@lambda = 106.208257, rho = 44.535886
> SSEM@lambda = 63.670177, rho = 44.535886
> SSEM@lambda = 38.169269, rho = 44.535886
> SSEM@lambda = 22.881875, rho = 44.535886
> SSEM@lambda = 13.717324, rho = 44.535886
> SSEM@lambda = 8.223320, rho = 44.535886
> SSEM@lambda = 4.929751, rho = 44.535886
> SSEM@lambda = 2.955308, rho = 44.535886
> SSEM@lambda = 1.771661, rho = 44.535886
> SSEM@lambda = 314.307563, rho = 26.698563
> SSEM@lambda = 188.422434, rho = 26.698563
> SSEM@lambda = 112.956281, rho = 26.698563
> SSEM@lambda = 67.715512, rho = 26.698563
> SSEM@lambda = 40.594383, rho = 26.698563
> SSEM@lambda = 24.335693, rho = 26.698563
> SSEM@lambda = 14.588865, rho = 26.698563
> SSEM@lambda = 8.745795, rho = 26.698563
> SSEM@lambda = 5.242966, rho = 26.698563
> SSEM@lambda = 3.143076, rho = 26.698563
> SSEM@lambda = 361.595415, rho = 16.005368
> SSEM@lambda = 216.770756, rho = 16.005368
> SSEM@lambda = 129.950654, rho = 16.005368
> SSEM@lambda = 77.903371, rho = 16.005368
> SSEM@lambda = 46.701844, rho = 16.005368
> SSEM@lambda = 27.997020, rho = 16.005368
> SSEM@lambda = 16.783772, rho = 16.005368
> SSEM@lambda = 10.061607, rho = 16.005368
> SSEM@lambda = 6.031775, rho = 16.005368
> SSEM@lambda = 3.615954, rho = 16.005368
> SSEM@lambda = 379.412389, rho = 9.594966
> SSEM@lambda = 227.451752, rho = 9.594966
> SSEM@lambda = 136.353743, rho = 9.594966
> SSEM@lambda = 81.741921, rho = 9.594966
> SSEM@lambda = 49.002994, rho = 9.594966
> SSEM@lambda = 29.376523, rho = 9.594966
> SSEM@lambda = 17.610763, rho = 9.594966
> SSEM@lambda = 10.557375, rho = 9.594966
> SSEM@lambda = 6.328980, rho = 9.594966
> SSEM@lambda = 3.794124, rho = 9.594966
> SSEM@lambda = 386.989634, rho = 5.752031
> SSEM@lambda = 231.994190, rho = 5.752031
> SSEM@lambda = 139.076863, rho = 5.752031
> SSEM@lambda = 83.374389, rho = 5.752031
> SSEM@lambda = 49.981633, rho = 5.752031
> SSEM@lambda = 29.963202, rho = 5.752031
> SSEM@lambda = 17.962468, rho = 5.752031
> SSEM@lambda = 10.768216, rho = 5.752031
> SSEM@lambda = 6.455376, rho = 5.752031
> SSEM@lambda = 3.869896, rho = 5.752031
> SSEM@lambda = 391.092890, rho = 3.448252
> SSEM@lambda = 234.454028, rho = 3.448252
> SSEM@lambda = 140.551497, rho = 3.448252
```

```
> SSEM@lambda = 84.258409, rho = 3.448252
> SSEM@lambda = 50.511589, rho = 3.448252
> SSEM@lambda = 30.280902, rho = 3.448252
> SSEM@lambda = 18.152924, rho = 3.448252
> SSEM@lambda = 10.882392, rho = 3.448252
> SSEM@lambda = 6.523823, rho = 3.448252
> SSEM@lambda = 3.910929, rho = 3.448252
> SSEM@lambda = 393.730044, rho = 2.067173
> SSEM@lambda = 236.034961, rho = 2.067173
> SSEM@lambda = 141.499241, rho = 2.067173
> SSEM@lambda = 84.826567, rho = 2.067173
> SSEM@lambda = 50.852191, rho = 2.067173
> SSEM@lambda = 30.485087, rho = 2.067173
> SSEM@lambda = 18.275330, rho = 2.067173
> SSEM@lambda = 10.955772, rho = 2.067173
> SSEM@lambda = 6.567813, rho = 2.067173
> SSEM@lambda = 3.937300, rho = 2.067173
> SSEM@lambda = 387.398451, rho = 1.239237
> SSEM@lambda = 232.239270, rho = 1.239237
> SSEM@lambda = 139.223785, rho = 1.239237
> SSEM@lambda = 83.462466, rho = 1.239237
> SSEM@lambda = 50.034434, rho = 1.239237
> SSEM@lambda = 29.994855, rho = 1.239237
> SSEM@lambda = 17.981443, rho = 1.239237
> SSEM@lambda = 10.779592, rho = 1.239237
> SSEM@lambda = 6.462196, rho = 1.239237
> SSEM@lambda = 3.873985, rho = 1.239237
> SSEM@lambda = 381.269630, rho = 0.742903
> SSEM@lambda = 228.565138, rho = 0.742903
> SSEM@lambda = 137.021201, rho = 0.742903
> SSEM@lambda = 82.142052, rho = 0.742903
> SSEM@lambda = 49.242866, rho = 0.742903
> SSEM@lambda = 29.520323, rho = 0.742903
> SSEM@lambda = 17.696969, rho = 0.742903
> SSEM@lambda = 10.609054, rho = 0.742903
> SSEM@lambda = 6.359961, rho = 0.742903
> SSEM@lambda = 3.812696, rho = 0.742903
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 = 1.207720,  logLik = 4945.893140
> SSEMQ     niter = 2,  relerr = 0.298789,  logLik = 2552.134060
> SSEMQ     niter = 3,  relerr = 0.069570,  logLik = 1931.860704
> SSEMQ     niter = 4,  relerr = 0.014078,  logLik = 1911.888998
> SSEMQ     niter = 5,  relerr = 0.008222,  logLik = 1689.321518
> SSEMQ     niter = 6,  relerr = 0.010398,  logLik = 1453.525216
> SSEMQ     niter = 7,  relerr = 0.008845,  logLik = 1296.058998
> SSEMQ     niter = 8,  relerr = 0.006533,  logLik = 1205.876484
> SSEMQ     niter = 9,  relerr = 0.004512,  logLik = 1146.440775
> SSEMQ     niter = 10,     relerr = 0.003075,  logLik = 1096.201308
> SSEMQ     niter = 11,     relerr = 0.002472,  logLik = 1051.226722
> SSEMQ     niter = 12,     relerr = 0.002614,  logLik = 1010.143130
```

```
> SSEMQ      niter = 13,      relerr = 0.002644,   logLik = 975.337346
> SSEMQ      niter = 14,      relerr = 0.002525,   logLik = 947.508923
> SSEMQ      niter = 15,      relerr = 0.002324,   logLik = 924.559287
> SSEMQ      niter = 16,      relerr = 0.002078,   logLik = 906.588419
> SSEMQ      niter = 17,      relerr = 0.001817,   logLik = 893.144808
> SSEMQ      niter = 18,      relerr = 0.001600,   logLik = 881.296357
> SSEMQ      niter = 19,      relerr = 0.001408,   logLik = 871.256749
> SSEMQ      niter = 20,      relerr = 0.001231,   logLik = 863.212528
> SSEMQ      niter = 21,      relerr = 0.001145,   logLik = 856.648375
> SSEMQ      niter = 22,      relerr = 0.001103,   logLik = 850.610517
> SSEMQ      niter = 23,      relerr = 0.001070,   logLik = 845.542679
> SSEMQ      niter = 24,      relerr = 0.001041,   logLik = 840.987015
> SSEMQ      niter = 25,      relerr = 0.001002,   logLik = 836.728939
> SSEMQ      niter = 26,      relerr = 0.000964,   logLik = 832.683185
> SSEMQ      niter = 27,      relerr = 0.000846,   logLik = 832.403133
> SSEMQ      niter = 28,      relerr = 0.000747,   logLik = 832.095341
> SSEMQ      niter = 29,      relerr = 0.000663,   logLik = 831.291406
> SSEMQ      niter = 30,      relerr = 0.000599,   logLik = 830.328826
> SSEMQ      niter = 31,      relerr = 0.000526,   logLik = 829.783808
> SSEMQ      niter = 32,      relerr = 0.000475,   logLik = 829.425745
> SSEMQ      niter = 33,      relerr = 0.000450,   logLik = 828.894487
> SSEMQ      niter = 34,      relerr = 0.000423,   logLik = 828.342866
> SSEMQ      niter = 35,      relerr = 0.000404,   logLik = 827.867186
> SSEMQ      niter = 36,      relerr = 0.000377,   logLik = 827.489061
> SSEMQ      niter = 37,      relerr = 0.000360,   logLik = 827.111711
> SSEMQ      niter = 38,      relerr = 0.000338,   logLik = 826.862593
> SSEMQ      niter = 39,      relerr = 0.000317,   logLik = 826.664596
> SSEMQ      niter = 40,      relerr = 0.000297,   logLik = 826.484258
> SSEMQ      niter = 41,      relerr = 0.000274,   logLik = 826.322177
> SSEMQ      niter = 42,      relerr = 0.000257,   logLik = 826.159428
> SSEMQ      niter = 43,      relerr = 0.000243,   logLik = 825.986386
> SSEMQ      niter = 44,      relerr = 0.000232,   logLik = 825.815585
> SSEMQ      niter = 45,      relerr = 0.000223,   logLik = 825.662609
> SSEMQ      niter = 46,      relerr = 0.000214,   logLik = 825.539608
> SSEMQ      niter = 47,      relerr = 0.000204,   logLik = 825.451543
> SSEMQ      niter = 48,      relerr = 0.000193,   logLik = 825.395713
> SSEMQ      niter = 49,      relerr = 0.000182,   logLik = 825.363875
> SSEMQ      niter = 50,      relerr = 0.000170,   logLik = 825.345608
> SSEMQ      niter = 51,      relerr = 0.000158,   logLik = 825.331511
> SSEMQ      niter = 52,      relerr = 0.000148,   logLik = 825.315251
> SSEMQ      niter = 53,      relerr = 0.000139,   logLik = 825.294138
> SSEMQ      niter = 54,      relerr = 0.000132,   logLik = 825.268436
> SSEMQ      niter = 55,      relerr = 0.000126,   logLik = 825.240010
> SSEMQ      niter = 56,      relerr = 0.000120,   logLik = 825.210934
> SSEMQ      niter = 57,      relerr = 0.000116,   logLik = 825.182553
> SSEMQ      niter = 58,      relerr = 0.000112,   logLik = 825.155181
> SSEMQ      niter = 59,      relerr = 0.000108,   logLik = 825.128374
> SSEMQ      niter = 60,      relerr = 0.000105,   logLik = 825.101491
> SSEMQ      niter = 61,      relerr = 0.000103,   logLik = 825.074275
> SSEMQ      niter = 62,      relerr = 0.000102,   logLik = 825.047178
> SSEMQ      niter = 63,      relerr = 0.000100,   logLik = 825.021355
> SSEMQ      niter = 64,      relerr = 0.000098,   logLik = 824.998353
> SSEMQ      niter = 65,      relerr = 0.000096,   logLik = 824.979648
```

```
> SSEMQ      niter = 66,      relerr = 0.000092,  logLik = 824.966185
> SSEMQ      niter = 67,      relerr = 0.000088,  logLik = 824.958097
> SSEMQ      niter = 68,      relerr = 0.000082,  logLik = 824.954652
> SSEMQ      niter = 69,      relerr = 0.000077,  logLik = 824.954440
> SSEMQ      niter = 70,      relerr = 0.000071,  logLik = 824.955713
> SSEMQ      niter = 71,      relerr = 0.000065,  logLik = 824.956772
> SSEMQ      niter = 72,      relerr = 0.000060,  logLik = 824.956309
> SSEMQ      niter = 73,      relerr = 0.000057,  logLik = 824.953608
> SSEMQ      niter = 74,      relerr = 0.000054,  logLik = 824.948591
> SSEMQ      niter = 75,      relerr = 0.000053,  logLik = 824.941718
> SSEMQ      niter = 76,      relerr = 0.000053,  logLik = 824.933792
> SSEMQ      niter = 77,      relerr = 0.000053,  logLik = 824.925735
> SSEMQ      niter = 78,      relerr = 0.000052,  logLik = 824.918382
> SSEMQ      niter = 79,      relerr = 0.000052,  logLik = 824.912343
> SSEMQ      niter = 80,      relerr = 0.000051,  logLik = 824.907925
> SSEMQ      niter = 81,      relerr = 0.000049,  logLik = 824.905147
> SSEMQ      niter = 82,      relerr = 0.000047,  logLik = 824.903782
> SSEMQ      niter = 83,      relerr = 0.000044,  logLik = 824.903450
> SSEMQ      niter = 84,      relerr = 0.000042,  logLik = 824.903699
> SSEMQ      niter = 85,      relerr = 0.000039,  logLik = 824.904082
> SSEMQ      niter = 86,      relerr = 0.000036,  logLik = 824.904218
> SSEMQ      niter = 87,      relerr = 0.000034,  logLik = 824.903827
> SSEMQ      niter = 88,      relerr = 0.000032,  logLik = 824.902746
> SSEMQ      niter = 89,      relerr = 0.000031,  logLik = 824.900934
> SSEMQ      niter = 90,      relerr = 0.000031,  logLik = 824.898460
> SSEMQ      niter = 91,      relerr = 0.000031,  logLik = 824.895482
> SSEMQ      niter = 92,      relerr = 0.000031,  logLik = 824.892220
> SSEMQ      niter = 93,      relerr = 0.000032,  logLik = 824.888927
> SSEMQ      niter = 94,      relerr = 0.000032,  logLik = 824.885854
> SSEMQ      niter = 95,      relerr = 0.000032,  logLik = 824.883216
> SSEMQ      niter = 96,      relerr = 0.000032,  logLik = 824.881167
> SSEMQ      niter = 97,      relerr = 0.000031,  logLik = 824.879779
> SSEMQ      niter = 98,      relerr = 0.000030,  logLik = 824.879042
> SSEMQ      niter = 99,      relerr = 0.000029,  logLik = 824.878864
> SSEMQ      niter = 100,     relerr = 0.000028,  logLik = 824.879093
> SSEMQ      niter = 101,     relerr = 0.000026,  logLik = 824.879540
> SSEMQ      niter = 102,     relerr = 0.000024,  logLik = 824.880008
> SSEMQ      niter = 103,     relerr = 0.000022,  logLik = 824.880320
> SSEMQ      niter = 104,     relerr = 0.000021,  logLik = 824.880337
> SSEMQ      niter = 105,     relerr = 0.000020,  logLik = 824.879980
> SSEMQ      niter = 106,     relerr = 0.000019,  logLik = 824.879224
> SSEMQ      niter = 107,     relerr = 0.000019,  logLik = 824.878102
> SSEMQ      niter = 108,     relerr = 0.000019,  logLik = 824.876690
> SSEMQ      niter = 109,     relerr = 0.000019,  logLik = 824.875096
> SSEMQ      niter = 110,     relerr = 0.000020,  logLik = 824.873436
> SSEMQ      niter = 111,     relerr = 0.000020,  logLik = 824.871826
> SSEMQ      niter = 112,     relerr = 0.000021,  logLik = 824.870364
> SSEMQ      niter = 113,     relerr = 0.000021,  logLik = 824.869124
> SSEMQ      niter = 114,     relerr = 0.000021,  logLik = 824.868146
> SSEMQ      niter = 115,     relerr = 0.000020,  logLik = 824.867440
> SSEMQ      niter = 116,     relerr = 0.000019,  logLik = 824.866986
> SSEMQ      niter = 117,     relerr = 0.000019,  logLik = 824.866741
> SSEMQ      niter = 118,     relerr = 0.000018,  logLik = 824.866648
```

```
> SSEMQ     niter = 119,    relerr = 0.000016,  logLik = 824.866642
> SSEMQ     niter = 120,    relerr = 0.000015,  logLik = 824.866662
> SSEMQ     niter = 121,    relerr = 0.000014,  logLik = 824.866655
> SSEMQ     niter = 122,    relerr = 0.000014,  logLik = 824.866587
> SSEMQ     niter = 123,    relerr = 0.000013,  logLik = 824.866439
> SSEMQ     niter = 124,    relerr = 0.000013,  logLik = 824.866211
> SSEMQ     niter = 125,    relerr = 0.000013,  logLik = 824.865921
> SSEMQ     niter = 126,    relerr = 0.000013,  logLik = 824.865596
> SSEMQ     niter = 127,    relerr = 0.000014,  logLik = 824.865271
> SSEMQ     niter = 128,    relerr = 0.000014,  logLik = 824.864980
> SSEMQ     niter = 129,    relerr = 0.000014,  logLik = 824.864753
> SSEMQ     niter = 130,    relerr = 0.000014,  logLik = 824.864611
> SSEMQ     niter = 131,    relerr = 0.000014,  logLik = 824.864562
> SSEMQ     niter = 132,    relerr = 0.000013,  logLik = 824.864604
> SSEMQ     niter = 133,    relerr = 0.000013,  logLik = 824.864725
> SSEMQ     niter = 134,    relerr = 0.000012,  logLik = 824.864902
> SSEMQ     niter = 135,    relerr = 0.000011,  logLik = 824.865112
> SSEMQ     niter = 136,    relerr = 0.000011,  logLik = 824.865326
> SSEMQ     niter = 137,    relerr = 0.000010,  logLik = 824.865523
> SSEMQ     niter = 138,    relerr = 0.000010,  logLik = 824.865683
> SSEMQ     niter = 139,    relerr = 0.000009,  logLik = 824.865797
> SSEMQ     niter = 140,    relerr = 0.000009,  logLik = 824.865860
> SSEMQ     niter = 141,    relerr = 0.000009,  logLik = 824.865877
> SSEMQ     niter = 142,    relerr = 0.000008,  logLik = 824.865857
> SSEMQ     niter = 143,    relerr = 0.000008,  logLik = 824.865814
> SSEMQ     niter = 144,    relerr = 0.000008,  logLik = 824.865762
> SSEMQ     niter = 145,    relerr = 0.000008,  logLik = 824.865714
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```

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> SSEMQ     niter = 276,    relerr = 0.000001,  logLik = 824.861211
> SSEMQ     niter = 277,    relerr = 0.000001,  logLik = 824.861206
```

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> SSEMQ     niter = 295,    relerr = 0.000001,  logLik = 824.861171
```

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 ="Recal
```

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[,
```

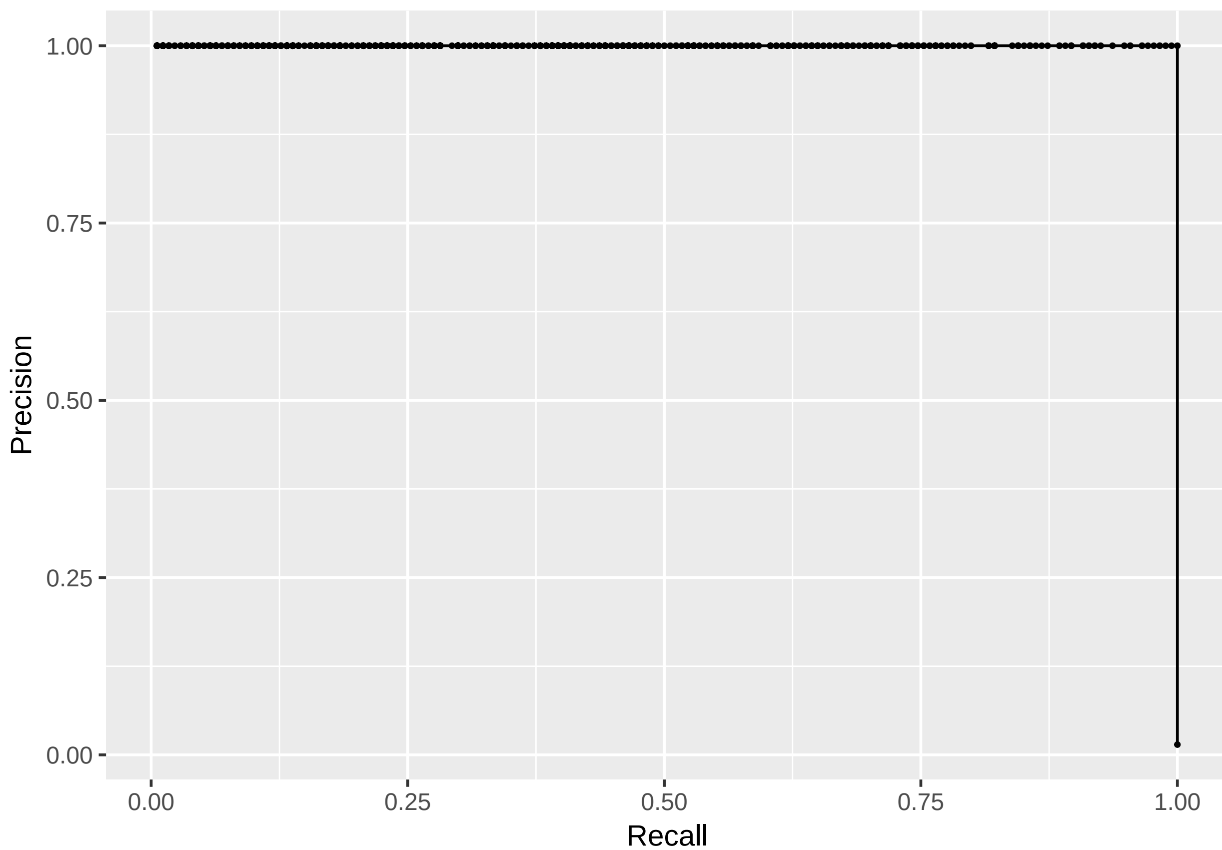

Figure 2: PR curve of trans-eQTL

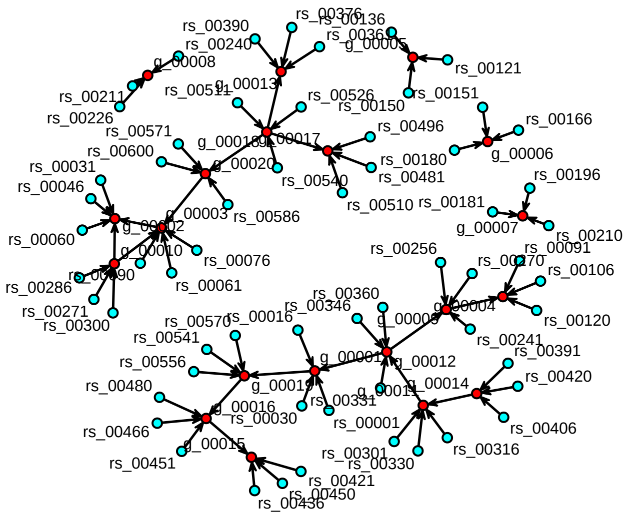

Figure 3: GRN QTL Network

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       iterators_1.0.9
>  [7] tools_3.4.0          digest_0.6.23        evaluate_0.14
```

```
> [10] tibble_1.3.0        lifecycle_0.1.0.9000 gtable_0.3.0
> [13] lattice_0.20-35     pkgconfig_2.0.3      rlang_0.4.4.9000
> [16] foreach_1.4.4       ggrepel_0.8.1        yaml_2.2.1
> [19] parallel_3.4.0      mvtnorm_1.0-8        xfun_0.12
> [22] coda_0.19-3         fssemR_0.1.6         stringr_1.4.0
> [25] knitr_1.28          RevoUtils_10.0.4     glmnet_2.0-8
> [28] grid_3.4.0          R6_2.4.1             rARPACK_0.11-0
> [31] qtl_1.45-11         rmarkdown_2.1        farver_2.0.3.9000
> [34] magrittr_1.5        scales_1.1.0.9000    codetools_0.2-15
> [37] htmltools_0.4.0     MASS_7.3-49          colorspace_1.4-1
> [40] labeling_0.3        stringi_1.4.5        lazyeval_0.2.2
> [43] munsell_0.5.0       statnet.common_4.1.4
```