ssemQr: Sparse Structural Equation Models based eQTL mapping

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

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
> g_00005   6.166067 13.5259890 -0.3794916 14.182132 -1.131211 -1.69599359
```

Figure 1: GRN QTL Network

```
> 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]
> g_00001  0.7487899   1.709192   8.899143  -4.688677  -3.635110  -2.942381
> g_00002  1.1270648  13.813581  16.189511   6.612697  16.296739   8.057332
> g_00003 -0.1060480  12.132866   5.869786  -3.944956   3.052335  -5.923862
> g_00004  8.8846909  17.339766   6.435624   1.199065   2.001491   4.167714
> g_00005  6.1864841  11.685948   8.692697   8.589368   3.678769   8.617383
> g_00006  9.8419935   2.368097  13.349509  -2.679751   1.746703   6.459423
>               [,19]       [,20]      [,21]       [,22]       [,23]       [,24]
> g_00001 -8.985299 -11.0318016   2.845532  -0.2116834  -2.1680930  -2.9761235
> g_00002  7.070144   0.6870488  11.270394  11.4006258   7.1345237   6.3313823
> g_00003 -3.610565  -0.8711937   3.234500  10.1033906   1.4730168  -0.4842867
> g_00004 10.821980   6.6255378   7.569950   0.0305707   1.4260755  11.8862314
> g_00005  3.765058   8.0242722   6.432018   8.7876071   0.5925095   6.2541864
> g_00006  1.672773   9.8121681   9.372386   1.5312734   1.7205105   1.8119920
>               [,25]       [,26]      [,27]      [,28]       [,29]      [,30]
> g_00001 -7.6594039 -10.8600777  -0.6530769  -0.414423  -0.5156778   6.598562
> g_00002  3.7034281  10.4724297  14.9394397  17.964168   4.3343203   7.673636
> g_00003 -1.8553575   3.0596264  10.7144885  -1.269667   0.8870281  -3.054480
> g_00004  8.9440674   0.7561117   8.9586460   4.980906   1.1137763   5.882877
> g_00005 -0.8474681   9.3922373   5.6270000  -1.064443   5.6756813   6.109425
> g_00006  1.4059919   5.9580352   5.7285995  -2.564782   4.9387256  10.022352
>               [,31]      [,32]      [,33]      [,34]      [,35]      [,36]
> g_00001  3.114266  -6.471673   7.3144230  -6.646288  -4.816060   2.103165
> g_00002 10.062633   6.631378  -0.4353275   3.718508   9.953127  10.467397
> g_00003  1.931242   6.091258  -9.3621655  -6.519739   6.718040   2.565498
> g_00004 13.101000   4.338571   2.8609885   8.757427  14.513295   8.692028
```

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```
> g_00005   3.791205   6.188368  -1.1023432   6.052601   8.653607   8.081071
> g_00006   1.227683   9.382513  -2.0088045   9.399975  10.093147   9.257986
>                 [,37]      [,38]       [,39]      [,40]       [,41]       [,42]
> g_00001   6.7238047   4.203827   -3.0060822  -1.134171  -12.6736888  -5.8349892
> g_00002  10.4952372  13.883943    0.1108343   9.061710    7.6852113  14.1420419
> g_00003  -0.2475049   7.121438  -10.7957793   0.114919   -0.2166458   0.3976376
> g_00004  13.4417498  14.060510    9.9425633   8.027816   10.4379657   7.8836556
> g_00005   6.0791392   9.228961    0.7059098   6.058761   -1.7728103  14.2017676
> g_00006   9.9098151  13.353713    5.2615153   5.603717    4.8875901  10.1416156
>                 [,43]      [,44]       [,45]     [,46]      [,47]      [,48]
> g_00001  -1.8656431  -2.024858   -1.933522  3.867380  -1.925601  -2.226472
> g_00002   5.7148266  11.469324   14.335534  7.587169  15.314490   8.195370
> g_00003  -4.9987882   8.874392    0.604662  4.121844   2.117166   1.632544
> g_00004   0.5374723   7.193962    6.492399  9.981586   7.526914   1.554155
> g_00005   5.9692886  -1.930270    1.298690  6.208491   1.418061   8.508896
> g_00006   5.1692746   4.855222    5.648892  2.027159   1.435545   9.479543
>                 [,49]      [,50]       [,51]      [,52]     [,53]      [,54]
> g_00001   5.3090633   1.916836  -2.4231929  -3.5473039  -4.393693   0.3921614
> g_00002  16.2872207   9.750388  10.9504148  11.9620802  11.437627  11.1966680
> g_00003   0.9915105   2.751724   0.5667139  -3.8307753   8.890505  -1.6812782
> g_00004   7.1437187  15.267246  10.2864788  -0.3620542  12.871005   8.8236845
> g_00005   3.7537718  -1.281104   9.3633607  13.3969300   8.587354  14.1236456
> g_00006   1.7009150   1.663106   9.3399113   6.3972207  -2.669502   9.4935484
>                 [,55]      [,56]       [,57]      [,58]      [,59]      [,60]
> g_00001   3.890589  -6.726872    5.942963  -1.053999  -11.195599  -5.768291
> g_00002  10.351887  13.469142   16.155706  17.443236   -5.246004  11.652374
> g_00003   5.005066   4.777561    5.095566  15.108740   -4.083751   2.027858
> g_00004  10.618419   6.444955   15.573605  12.087122   13.043358   6.707587
> g_00005   6.266269   6.283303    3.813854   1.322333    3.259035  11.069753
> g_00006   5.512256   2.081688   -1.938316   5.738951    1.992011   6.235394
>                 [,61]      [,62]       [,63]       [,64]      [,65]      [,66]
> g_00001   5.060398   8.7749914    4.056718  -11.7286004  -2.978133  -1.950763
> g_00002   8.216822  16.4001093   15.751575    7.8079298  14.146234  12.269135
> g_00003  -3.299455  -3.0149797    2.986897   -0.6390034  -2.376841   3.047890
> g_00004   9.393615   4.5066203    9.444174   -3.0088597   9.285481  13.710103
> g_00005   1.240651  -0.3639891   -1.114934    7.8536911   6.109719   5.575372
> g_00006   6.058027   1.6109180    1.644187    5.5773164   6.130370   5.667780
>                 [,67]      [,68]       [,69]      [,70]      [,71]      [,72]
> g_00001   4.502137    0.7128866  -1.7423517   0.6437823   3.204284   8.126654
> g_00002  13.572292   -2.7733150   0.7019292  14.1809632   2.631195   7.206733
> g_00003   4.381545  -11.8750191  -9.5438658  -0.7949477  -6.985166 -11.300990
> g_00004   9.359436    2.3853670   9.9105672  15.1429150   6.096830   1.121800
> g_00005   6.161236    9.3143839   3.1989699  11.0601977   3.937240  -1.680335
> g_00006   5.667409   10.0227647   5.4201123   1.9883107   1.172539   9.417599
>                 [,73]      [,74]       [,75]      [,76]      [,77]      [,78]
> g_00001  -1.544988  -1.31803901   -1.433919   1.384086  0.3878227   1.2264747
> g_00002   6.423605  12.86863858    9.010747   7.645500  6.7227010   8.9927746
> g_00003  -5.791771   0.02377311   -4.602436  -8.878113  2.1070564  -8.6819711
> g_00004  -4.578092   2.19404512    8.410683   7.535253  6.1500404  -0.7263027
> g_00005   5.628887   7.72330860    9.407079   6.069205  5.3864538   8.5552216
> g_00006  -2.518401   9.68875483    5.797374   9.848149  9.8118246  10.2990689
>                 [,79]      [,80]       [,81]      [,82]      [,83]      [,84]
> g_00001   4.304476  -2.5372381   -1.112774  -7.923377  -4.249496  -0.4036571
```

4

```
> g_00002 18.558877   9.2040634   7.421554   -5.127343 10.003278   6.1962004
> g_00003   4.701564  -0.3407032   3.681131 -14.115413   3.918818  -0.7920674
> g_00004 13.323989   9.8980301 18.602395    5.700684 11.438041   3.6336251
> g_00005   6.055221   8.6557686   9.357022    8.065133   3.848850   2.9987655
> g_00006   8.943252 13.6588664   1.819483    5.856623   1.116631   4.7920443
>              [,85]       [,86]       [,87]       [,88]       [,89]       [,90]
> g_00001  -2.701486 -13.104847  -1.5264872  -7.6580429  -1.615780  -5.119185
> g_00002   9.266007   14.269113 14.2560830  -0.5561409 15.671043 11.592149
> g_00003   3.193766   10.098628  -3.1187153  -4.9693846  -1.424904   1.213970
> g_00004   6.713172   -1.260435  -0.2156557   7.6892550   7.337562   6.691697
> g_00005   4.584526   12.796822  -1.6794919 13.4044095   6.115046 13.685374
> g_00006   1.116494    5.417585   1.6985779 10.2497881   5.659739 13.888826
>              [,91]       [,92]       [,93]       [,94]       [,95]       [,96]
> g_00001   4.237222   2.229065  -0.2066921   2.0818405   1.716663   0.8116527
> g_00002   4.913900   8.238007 10.0928720 15.3091971 17.123965 13.5271154
> g_00003  -1.772840  -7.786742  -0.2133384   0.4061676   6.721378   4.8479400
> g_00004   8.422380   7.081328   5.0635455   9.0410206   6.427174   7.6497027
> g_00005   3.914024 14.170359  -1.8505320 11.7049881 11.114235  -1.8487619
> g_00006   5.589979   9.821148   1.5750276   5.6813180   5.707217   1.5968447
>              [,97]       [,98]       [,99]     [,100]
> g_00001  -0.5738103   3.401589   4.173171   1.525293
> g_00002   9.3686685 18.328054 11.029991   5.203210
> g_00003  -1.5629534   5.037280   0.806792  -2.476404
> g_00004   7.8937133 10.206356 14.258247 11.295805
> g_00005   8.0275200 11.730174   6.002121   7.047583
> g_00006 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]
> rs_00001    1    2    1    2    1    0    1    2    0     2     1     2
> rs_00002    1    2    1    2    1    0    0    2    0     1     1     2
> rs_00003    1    2    1    2    1    0    0    2    0     1     0     2
> rs_00004    1    2    1    2    1    0    0    2    0     1     0     2
> rs_00005    1    2    1    2    1    0    0    2    0     1     0     2
> rs_00006    1    2    2    2    1    0    0    2    0     1     0     2
>         [,13] [,14] [,15] [,16] [,17] [,18] [,19] [,20] [,21] [,22] [,23]
> rs_00001     1     1     2     1     0     1     0     1     1     2     0
> rs_00002     0     1     2     1     1     1     0     1     1     2     1
> rs_00003     0     1     2     1     1     1     0     1     1     2     1
> rs_00004     1     1     2     1     1     1     0     1     1     2     1
> rs_00005     1     1     2     1     1     1     0     1     1     2     1
> rs_00006     1     1     2     1     1     1     0     1     2     2     1
>         [,24] [,25] [,26] [,27] [,28] [,29] [,30] [,31] [,32] [,33] [,34]
> rs_00001     1     0     0     1     2     2     2     2     1     2     0
> rs_00002     1     0     0     1     1     1     2     2     1     2     0
> rs_00003     1     0     0     1     1     1     2     2     1     2     0
> rs_00004     1     0     0     0     1     1     2     2     1     2     0
> rs_00005     1     0     0     0     1     1     2     2     1     2     0
> rs_00006     2     0     0     0     1     1     2     2     1     2     0
>         [,35] [,36] [,37] [,38] [,39] [,40] [,41] [,42] [,43] [,44] [,45]
> rs_00001     1     1     2     2     1     1     0     1     1     1     1
> rs_00002     1     1     2     2     1     1     0     1     1     1     1
```

```
> rs_00003      1      1      2      2      1      1      0      1      2      1      1
> rs_00004      1      1      2      2      1      1      0      1      2      1      1
> rs_00005      1      1      2      2      1      1      0      1      2      1      1
> rs_00006      1      1      2      2      1      1      0      1      1      0      1
>           [,46]  [,47]  [,48]  [,49]  [,50]  [,51]  [,52]  [,53]  [,54]  [,55]  [,56]
> rs_00001      1      1      0      2      1      1      0      0      2      2      1
> rs_00002      2      1      0      2      1      1      0      0      2      2      1
> rs_00003      2      1      0      2      1      1      0      0      2      2      1
> rs_00004      2      1      0      2      1      1      0      0      2      2      1
> rs_00005      2      1      0      2      1      1      0      0      2      2      1
> rs_00006      2      1      0      2      1      1      0      0      2      2      1
>           [,57]  [,58]  [,59]  [,60]  [,61]  [,62]  [,63]  [,64]  [,65]  [,66]  [,67]
> rs_00001      2      1      0      0      2      2      2      1      1      0      2
> rs_00002      2      1      0      0      2      2      2      1      1      0      2
> rs_00003      2      0      0      0      2      1      2      1      1      0      2
> rs_00004      2      0      0      0      2      1      2      0      1      0      2
> rs_00005      2      0      0      0      2      1      2      0      1      0      2
> rs_00006      2      0      0      0      2      1      2      0      1      0      2
>           [,68]  [,69]  [,70]  [,71]  [,72]  [,73]  [,74]  [,75]  [,76]  [,77]  [,78]
> rs_00001      1      1      1      1      2      2      2      1      1      2      2
> rs_00002      1      1      1      1      2      2      2      1      1      2      2
> rs_00003      1      1      1      1      2      2      2      1      1      2      2
> rs_00004      1      1      1      1      2      2      2      1      1      2      1
> rs_00005      2      1      1      1      2      2      2      1      1      2      1
> rs_00006      2      1      1      1      2      2      2      1      1      2      1
>           [,79]  [,80]  [,81]  [,82]  [,83]  [,84]  [,85]  [,86]  [,87]  [,88]  [,89]
> rs_00001      1      2      2      0      1      2      0      0      0      1      1
> rs_00002      1      1      2      0      1      2      0      0      0      1      1
> rs_00003      1      1      2      0      1      2      0      0      1      1      1
> rs_00004      1      1      2      0      1      2      0      0      2      0      2
> rs_00005      1      1      2      0      1      2      1      0      2      0      2
> rs_00006      1      1      2      0      1      2      1      0      2      0      2
>           [,90]  [,91]  [,92]  [,93]  [,94]  [,95]  [,96]  [,97]  [,98]  [,99]
> rs_00001      1      2      1      1      1      0      0      0      0      1
> rs_00002      1      1      1      1      1      0      0      0      0      1
> rs_00003      1      1      1      1      1      0      0      0      0      1
> rs_00004      1      1      1      1      1      0      0      0      0      1
> rs_00005      1      1      2      1      1      0      0      0      0      1
> rs_00006      1      1      2      1      1      0      0      0      0      1
>           [,100]
> rs_00001      2
> rs_00002      2
> rs_00003      2
> rs_00004      1
> rs_00005      1
> rs_00006      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] 24 25 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
> [24] 54 55 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
> [24] 84 85 86 87 88 89 90
>
> [[4]]
>  [1]  91  92  93  94  95  96  97  98  99 100 101 102 103 104 105 106 107
> [18] 108 109 110 111 112 113 114 115 116 117 118 119 120
>
> [[5]]
>  [1] 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137
> [18] 138 139 140 141 142 143 144 145 146 147 148 149 150
>
> [[6]]
>  [1] 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167
> [18] 168 169 170 171 172 173 174 175 176 177 178 179 180
```

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 = 100, nfold = 10, data$Vars$n, data$Vars$p, data$Vars$q)
>    [1] 6.3522574 6.2507156 6.1439930 6.0324521 5.9165073 5.7966113 5.6732394
>    [8] 5.5468767 5.4180058 5.2870996 5.1546170 5.0210037 4.8866971 4.7521324
>   [15] 4.6177527 4.4840154 4.3513991 4.2204045 4.0915513 3.9653680 3.8423790
>   [22] 3.7230828 3.6079310 3.4973031 3.3914844 3.2906459 3.1948307 3.1039484
>   [29] 3.0177765 2.9359721 2.8580894 2.7836054 2.7119483 2.6425268 2.5747611
>   [36] 2.5081078 2.4420822 2.3762762 2.3103690 2.2441320 2.1774298 2.1102152
>   [43] 2.0425208 1.9744459 1.9061441 1.8378049 1.7696424 1.7018774 1.6347289
>   [50] 1.5684012 1.5030821 1.4389350 1.3761012 1.3147002 1.2548290 1.1965683
>   [57] 1.1399806 1.0851192 1.0320220 0.9807181 0.9312308 0.8835738 0.8377552
>   [64] 0.7937793 0.7516502 0.7113628 0.6729146 0.6363108 0.6015428 0.5686167
>   [71] 0.5375372 0.5083024 0.4809286 0.4554202 0.4317874 0.4100311 0.3901532
>   [78] 0.3721385 0.3559648 0.3415844 0.3289407 0.3179365 0.3084878 0.3004579
>   [85] 0.2937241 0.2881442 0.2835858 0.2798914 0.2769299 0.2746041 0.2727766
>   [92] 0.2713580 0.2702884 0.2694663 0.2688706 0.2683959 0.2681146 0.2678791
>   [99] 0.2677509 0.2675926
fit0  = ridgeRegression(X, Y, Sk, gamma, data$Vars$n, data$Vars$p, data$Vars$q, trans = FALSE, sparse
```

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$sigma2,
                       nlambda = 7, nrho = 7, p = data$Vars$p, wt = TRUE)
> SSEM@lambda = 51.870637, rho = 74.290202
> SSEM@lambda = 16.402936, rho = 74.290202
> SSEM@lambda = 5.187064, rho = 74.290202
> SSEM@lambda = 1.640294, rho = 74.290202
> SSEM@lambda = 0.518706, rho = 74.290202
> SSEM@lambda = 0.164029, rho = 74.290202
> SSEM@lambda = 0.051871, rho = 74.290202
> SSEM@lambda = 273.633043, rho = 23.492625
> SSEM@lambda = 86.530366, rho = 23.492625
> SSEM@lambda = 27.363304, rho = 23.492625
> SSEM@lambda = 8.653037, rho = 23.492625
> SSEM@lambda = 2.736330, rho = 23.492625
> SSEM@lambda = 0.865304, rho = 23.492625
> SSEM@lambda = 0.273633, rho = 23.492625
> SSEM@lambda = 325.878545, rho = 7.429020
> SSEM@lambda = 103.051844, rho = 7.429020
> SSEM@lambda = 32.587854, rho = 7.429020
> SSEM@lambda = 10.305184, rho = 7.429020
> SSEM@lambda = 3.258785, rho = 7.429020
> SSEM@lambda = 1.030518, rho = 7.429020
> SSEM@lambda = 0.325879, rho = 7.429020
> SSEM@lambda = 335.101519, rho = 2.349262
> SSEM@lambda = 105.968405, rho = 2.349262
> SSEM@lambda = 33.510152, rho = 2.349262
> SSEM@lambda = 10.596840, rho = 2.349262
> SSEM@lambda = 3.351015, rho = 2.349262
> SSEM@lambda = 1.059684, rho = 2.349262
> SSEM@lambda = 0.335102, rho = 2.349262
> SSEM@lambda = 323.162488, rho = 0.742902
> SSEM@lambda = 102.192952, rho = 0.742902
> SSEM@lambda = 32.316249, rho = 0.742902
> SSEM@lambda = 10.219295, rho = 0.742902
> SSEM@lambda = 3.231625, rho = 0.742902
> SSEM@lambda = 1.021930, rho = 0.742902
> SSEM@lambda = 0.323162, rho = 0.742902
> SSEM@lambda = 318.851306, rho = 0.234926
> SSEM@lambda = 100.829636, rho = 0.234926
> SSEM@lambda = 31.885131, rho = 0.234926
> SSEM@lambda = 10.082964, rho = 0.234926
> SSEM@lambda = 3.188513, rho = 0.234926
> SSEM@lambda = 1.008296, rho = 0.234926
> SSEM@lambda = 0.318851, rho = 0.234926
> SSEM@lambda = 332.715189, rho = 0.074290
> SSEM@lambda = 105.213781, rho = 0.074290
> SSEM@lambda = 33.271519, rho = 0.074290
> SSEM@lambda = 10.521378, rho = 0.074290
> SSEM@lambda = 3.327152, rho = 0.074290
> SSEM@lambda = 1.052138, rho = 0.074290
> SSEM@lambda = 0.332715, 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 = 0.895967,  logLik = 6150.677191
> SSEMQ     niter = 2,  relerr = 0.354813,  logLik = 5278.927954
> SSEMQ     niter = 3,  relerr = 0.160027,  logLik = 4261.989548
> SSEMQ     niter = 4,  relerr = 0.074771,  logLik = 3650.654591
> SSEMQ     niter = 5,  relerr = 0.034103,  logLik = 3493.288094
> SSEMQ     niter = 6,  relerr = 0.015237,  logLik = 3334.760204
> SSEMQ     niter = 7,  relerr = 0.009916,  logLik = 3094.711895
> SSEMQ     niter = 8,  relerr = 0.010957,  logLik = 2827.542307
> SSEMQ     niter = 9,  relerr = 0.010488,  logLik = 2590.033975
> SSEMQ     niter = 10,    relerr = 0.008996,  logLik = 2410.652824
> SSEMQ     niter = 11,    relerr = 0.007299,  logLik = 2284.873273
> SSEMQ     niter = 12,    relerr = 0.005846,  logLik = 2194.234866
> SSEMQ     niter = 13,    relerr = 0.004800,  logLik = 2125.252899
> SSEMQ     niter = 14,    relerr = 0.004179,  logLik = 2072.940685
> SSEMQ     niter = 15,    relerr = 0.003847,  logLik = 2029.122534
> SSEMQ     niter = 16,    relerr = 0.003559,  logLik = 1991.412641
> SSEMQ     niter = 17,    relerr = 0.003283,  logLik = 1961.926872
> SSEMQ     niter = 18,    relerr = 0.002970,  logLik = 1941.077609
> SSEMQ     niter = 19,    relerr = 0.002674,  logLik = 1924.172491
> SSEMQ     niter = 20,    relerr = 0.002369,  logLik = 1910.758834
> SSEMQ     niter = 21,    relerr = 0.002078,  logLik = 1902.394435
> SSEMQ     niter = 22,    relerr = 0.001749,  logLik = 1898.661316
> SSEMQ     niter = 23,    relerr = 0.001490,  logLik = 1896.698148
> SSEMQ     niter = 24,    relerr = 0.001295,  logLik = 1894.468941
> SSEMQ     niter = 25,    relerr = 0.001112,  logLik = 1893.076773
> SSEMQ     niter = 26,    relerr = 0.000965,  logLik = 1892.646754
> SSEMQ     niter = 27,    relerr = 0.000872,  logLik = 1891.508263
> SSEMQ     niter = 28,    relerr = 0.000814,  logLik = 1889.914696
> SSEMQ     niter = 29,    relerr = 0.000785,  logLik = 1887.864380
> SSEMQ     niter = 30,    relerr = 0.000764,  logLik = 1885.699751
> SSEMQ     niter = 31,    relerr = 0.000739,  logLik = 1883.672881
> SSEMQ     niter = 32,    relerr = 0.000723,  logLik = 1881.820763
> SSEMQ     niter = 33,    relerr = 0.000698,  logLik = 1880.277368
> SSEMQ     niter = 34,    relerr = 0.000663,  logLik = 1879.109190
> SSEMQ     niter = 35,    relerr = 0.000619,  logLik = 1878.312051
> SSEMQ     niter = 36,    relerr = 0.000570,  logLik = 1877.829701
> SSEMQ     niter = 37,    relerr = 0.000519,  logLik = 1877.577723
> SSEMQ     niter = 38,    relerr = 0.000471,  logLik = 1877.465977
> SSEMQ     niter = 39,    relerr = 0.000427,  logLik = 1877.415257
> SSEMQ     niter = 40,    relerr = 0.000390,  logLik = 1877.366566
> SSEMQ     niter = 41,    relerr = 0.000360,  logLik = 1877.283638
> SSEMQ     niter = 42,    relerr = 0.000337,  logLik = 1877.150607
> SSEMQ     niter = 43,    relerr = 0.000321,  logLik = 1876.967117
> SSEMQ     niter = 44,    relerr = 0.000310,  logLik = 1876.742825
> SSEMQ     niter = 45,    relerr = 0.000303,  logLik = 1876.492586
> SSEMQ     niter = 46,    relerr = 0.000299,  logLik = 1876.232893
> SSEMQ     niter = 47,    relerr = 0.000295,  logLik = 1875.979536
> SSEMQ     niter = 48,    relerr = 0.000291,  logLik = 1875.746190
> SSEMQ     niter = 49,    relerr = 0.000286,  logLik = 1875.543543
> SSEMQ     niter = 50,    relerr = 0.000278,  logLik = 1875.378729
```

```
> SSEMQ    niter = 51,    relerr = 0.000268,  logLik = 1875.254951
> SSEMQ    niter = 52,    relerr = 0.000255,  logLik = 1875.171388
> SSEMQ    niter = 53,    relerr = 0.000240,  logLik = 1875.123472
> SSEMQ    niter = 54,    relerr = 0.000223,  logLik = 1875.103609
> SSEMQ    niter = 55,    relerr = 0.000206,  logLik = 1875.102310
> SSEMQ    niter = 56,    relerr = 0.000189,  logLik = 1875.109573
> SSEMQ    niter = 57,    relerr = 0.000173,  logLik = 1875.116241
> SSEMQ    niter = 58,    relerr = 0.000159,  logLik = 1875.115194
> SSEMQ    niter = 59,    relerr = 0.000148,  logLik = 1875.102146
> SSEMQ    niter = 60,    relerr = 0.000140,  logLik = 1875.075786
> SSEMQ    niter = 61,    relerr = 0.000136,  logLik = 1875.037450
> SSEMQ    niter = 62,    relerr = 0.000133,  logLik = 1874.990418
> SSEMQ    niter = 63,    relerr = 0.000132,  logLik = 1874.938995
> SSEMQ    niter = 64,    relerr = 0.000132,  logLik = 1874.887605
> SSEMQ    niter = 65,    relerr = 0.000131,  logLik = 1874.840047
> SSEMQ    niter = 66,    relerr = 0.000130,  logLik = 1874.799007
> SSEMQ    niter = 67,    relerr = 0.000128,  logLik = 1874.765872
> SSEMQ    niter = 68,    relerr = 0.000125,  logLik = 1874.740782
> SSEMQ    niter = 69,    relerr = 0.000120,  logLik = 1874.722880
> SSEMQ    niter = 70,    relerr = 0.000115,  logLik = 1874.710643
> SSEMQ    niter = 71,    relerr = 0.000109,  logLik = 1874.702233
> SSEMQ    niter = 72,    relerr = 0.000103,  logLik = 1874.695804
> SSEMQ    niter = 73,    relerr = 0.000097,  logLik = 1874.689735
> SSEMQ    niter = 74,    relerr = 0.000091,  logLik = 1874.682790
> SSEMQ    niter = 75,    relerr = 0.000086,  logLik = 1874.674187
> SSEMQ    niter = 76,    relerr = 0.000083,  logLik = 1874.663614
> SSEMQ    niter = 77,    relerr = 0.000080,  logLik = 1874.651191
> SSEMQ    niter = 78,    relerr = 0.000079,  logLik = 1874.637391
> SSEMQ    niter = 79,    relerr = 0.000078,  logLik = 1874.622934
> SSEMQ    niter = 80,    relerr = 0.000078,  logLik = 1874.608663
> SSEMQ    niter = 81,    relerr = 0.000078,  logLik = 1874.595423
> SSEMQ    niter = 82,    relerr = 0.000077,  logLik = 1874.583937
> SSEMQ    niter = 83,    relerr = 0.000075,  logLik = 1874.574722
> SSEMQ    niter = 84,    relerr = 0.000074,  logLik = 1874.568024
> SSEMQ    niter = 85,    relerr = 0.000071,  logLik = 1874.563812
> SSEMQ    niter = 86,    relerr = 0.000068,  logLik = 1874.561798
> SSEMQ    niter = 87,    relerr = 0.000065,  logLik = 1874.561500
> SSEMQ    niter = 88,    relerr = 0.000061,  logLik = 1874.562325
> SSEMQ    niter = 89,    relerr = 0.000057,  logLik = 1874.563644
> SSEMQ    niter = 90,    relerr = 0.000054,  logLik = 1874.564886
> SSEMQ    niter = 91,    relerr = 0.000051,  logLik = 1874.565599
> SSEMQ    niter = 92,    relerr = 0.000048,  logLik = 1874.565486
> SSEMQ    niter = 93,    relerr = 0.000046,  logLik = 1874.564418
> SSEMQ    niter = 94,    relerr = 0.000044,  logLik = 1874.562411
> SSEMQ    niter = 95,    relerr = 0.000043,  logLik = 1874.559594
> SSEMQ    niter = 96,    relerr = 0.000042,  logLik = 1874.556164
> SSEMQ    niter = 97,    relerr = 0.000042,  logLik = 1874.552348
> SSEMQ    niter = 98,    relerr = 0.000042,  logLik = 1874.548367
> SSEMQ    niter = 99,    relerr = 0.000041,  logLik = 1874.544409
> SSEMQ    niter = 100,   relerr = 0.000041,  logLik = 1874.540616
> SSEMQ    niter = 101,   relerr = 0.000041,  logLik = 1874.537078
> SSEMQ    niter = 102,   relerr = 0.000040,  logLik = 1874.533841
> SSEMQ    niter = 103,   relerr = 0.000039,  logLik = 1874.530914
```

```
> SSEMQ     niter = 104,    relerr = 0.000039,   logLik = 1874.528282
> SSEMQ     niter = 105,    relerr = 0.000038,   logLik = 1874.525917
> SSEMQ     niter = 106,    relerr = 0.000037,   logLik = 1874.523788
> SSEMQ     niter = 107,    relerr = 0.000036,   logLik = 1874.521871
> SSEMQ     niter = 108,    relerr = 0.000035,   logLik = 1874.520145
> SSEMQ     niter = 109,    relerr = 0.000034,   logLik = 1874.518597
> SSEMQ     niter = 110,    relerr = 0.000033,   logLik = 1874.517218
> SSEMQ     niter = 111,    relerr = 0.000033,   logLik = 1874.515997
> SSEMQ     niter = 112,    relerr = 0.000031,   logLik = 1874.514919
> SSEMQ     niter = 113,    relerr = 0.000030,   logLik = 1874.513961
> SSEMQ     niter = 114,    relerr = 0.000029,   logLik = 1874.513093
> SSEMQ     niter = 115,    relerr = 0.000028,   logLik = 1874.512276
> SSEMQ     niter = 116,    relerr = 0.000027,   logLik = 1874.511467
> SSEMQ     niter = 117,    relerr = 0.000026,   logLik = 1874.510621
> SSEMQ     niter = 118,    relerr = 0.000025,   logLik = 1874.509703
> SSEMQ     niter = 119,    relerr = 0.000025,   logLik = 1874.508683
> SSEMQ     niter = 120,    relerr = 0.000024,   logLik = 1874.507550
> SSEMQ     niter = 121,    relerr = 0.000024,   logLik = 1874.506307
> SSEMQ     niter = 122,    relerr = 0.000024,   logLik = 1874.504974
> SSEMQ     niter = 123,    relerr = 0.000024,   logLik = 1874.503583
> SSEMQ     niter = 124,    relerr = 0.000024,   logLik = 1874.502178
> SSEMQ     niter = 125,    relerr = 0.000024,   logLik = 1874.500806
> SSEMQ     niter = 126,    relerr = 0.000024,   logLik = 1874.499512
> SSEMQ     niter = 127,    relerr = 0.000024,   logLik = 1874.498334
> SSEMQ     niter = 128,    relerr = 0.000024,   logLik = 1874.497298
> SSEMQ     niter = 129,    relerr = 0.000023,   logLik = 1874.496416
> SSEMQ     niter = 130,    relerr = 0.000023,   logLik = 1874.495687
> SSEMQ     niter = 131,    relerr = 0.000022,   logLik = 1874.495094
> SSEMQ     niter = 132,    relerr = 0.000021,   logLik = 1874.494611
> SSEMQ     niter = 133,    relerr = 0.000020,   logLik = 1874.494205
> SSEMQ     niter = 134,    relerr = 0.000019,   logLik = 1874.493839
> SSEMQ     niter = 135,    relerr = 0.000018,   logLik = 1874.493480
> SSEMQ     niter = 136,    relerr = 0.000018,   logLik = 1874.493099
> SSEMQ     niter = 137,    relerr = 0.000017,   logLik = 1874.492679
> SSEMQ     niter = 138,    relerr = 0.000016,   logLik = 1874.492209
> SSEMQ     niter = 139,    relerr = 0.000016,   logLik = 1874.491692
> SSEMQ     niter = 140,    relerr = 0.000016,   logLik = 1874.491139
> SSEMQ     niter = 141,    relerr = 0.000016,   logLik = 1874.490569
> SSEMQ     niter = 142,    relerr = 0.000016,   logLik = 1874.490005
> SSEMQ     niter = 143,    relerr = 0.000016,   logLik = 1874.489472
> SSEMQ     niter = 144,    relerr = 0.000016,   logLik = 1874.488993
> SSEMQ     niter = 145,    relerr = 0.000016,   logLik = 1874.488587
> SSEMQ     niter = 146,    relerr = 0.000016,   logLik = 1874.488267
> SSEMQ     niter = 147,    relerr = 0.000015,   logLik = 1874.488038
> SSEMQ     niter = 148,    relerr = 0.000015,   logLik = 1874.487898
> SSEMQ     niter = 149,    relerr = 0.000015,   logLik = 1874.487841
> SSEMQ     niter = 150,    relerr = 0.000014,   logLik = 1874.487852
> SSEMQ     niter = 151,    relerr = 0.000014,   logLik = 1874.487915
> SSEMQ     niter = 152,    relerr = 0.000013,   logLik = 1874.488011
> SSEMQ     niter = 153,    relerr = 0.000013,   logLik = 1874.488124
> SSEMQ     niter = 154,    relerr = 0.000012,   logLik = 1874.488238
> SSEMQ     niter = 155,    relerr = 0.000012,   logLik = 1874.488343
> SSEMQ     niter = 156,    relerr = 0.000011,   logLik = 1874.488429
```

```
> SSEMQ     niter = 157,    relerr = 0.000011,   logLik = 1874.488494
> SSEMQ     niter = 158,    relerr = 0.000011,   logLik = 1874.488538
> SSEMQ     niter = 159,    relerr = 0.000011,   logLik = 1874.488562
> SSEMQ     niter = 160,    relerr = 0.000010,   logLik = 1874.488571
> SSEMQ     niter = 161,    relerr = 0.000010,   logLik = 1874.488569
> SSEMQ     niter = 162,    relerr = 0.000010,   logLik = 1874.488561
> SSEMQ     niter = 163,    relerr = 0.000010,   logLik = 1874.488551
> SSEMQ     niter = 164,    relerr = 0.000010,   logLik = 1874.488539
> SSEMQ     niter = 165,    relerr = 0.000009,   logLik = 1874.488525
> SSEMQ     niter = 166,    relerr = 0.000009,   logLik = 1874.488509
> SSEMQ     niter = 167,    relerr = 0.000009,   logLik = 1874.488486
> SSEMQ     niter = 168,    relerr = 0.000009,   logLik = 1874.488454
> SSEMQ     niter = 169,    relerr = 0.000008,   logLik = 1874.488408
> SSEMQ     niter = 170,    relerr = 0.000008,   logLik = 1874.488344
> SSEMQ     niter = 171,    relerr = 0.000008,   logLik = 1874.488261
> SSEMQ     niter = 172,    relerr = 0.000008,   logLik = 1874.488157
> SSEMQ     niter = 173,    relerr = 0.000007,   logLik = 1874.488033
> SSEMQ     niter = 174,    relerr = 0.000007,   logLik = 1874.487888
> SSEMQ     niter = 175,    relerr = 0.000007,   logLik = 1874.487726
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```

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```

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
```
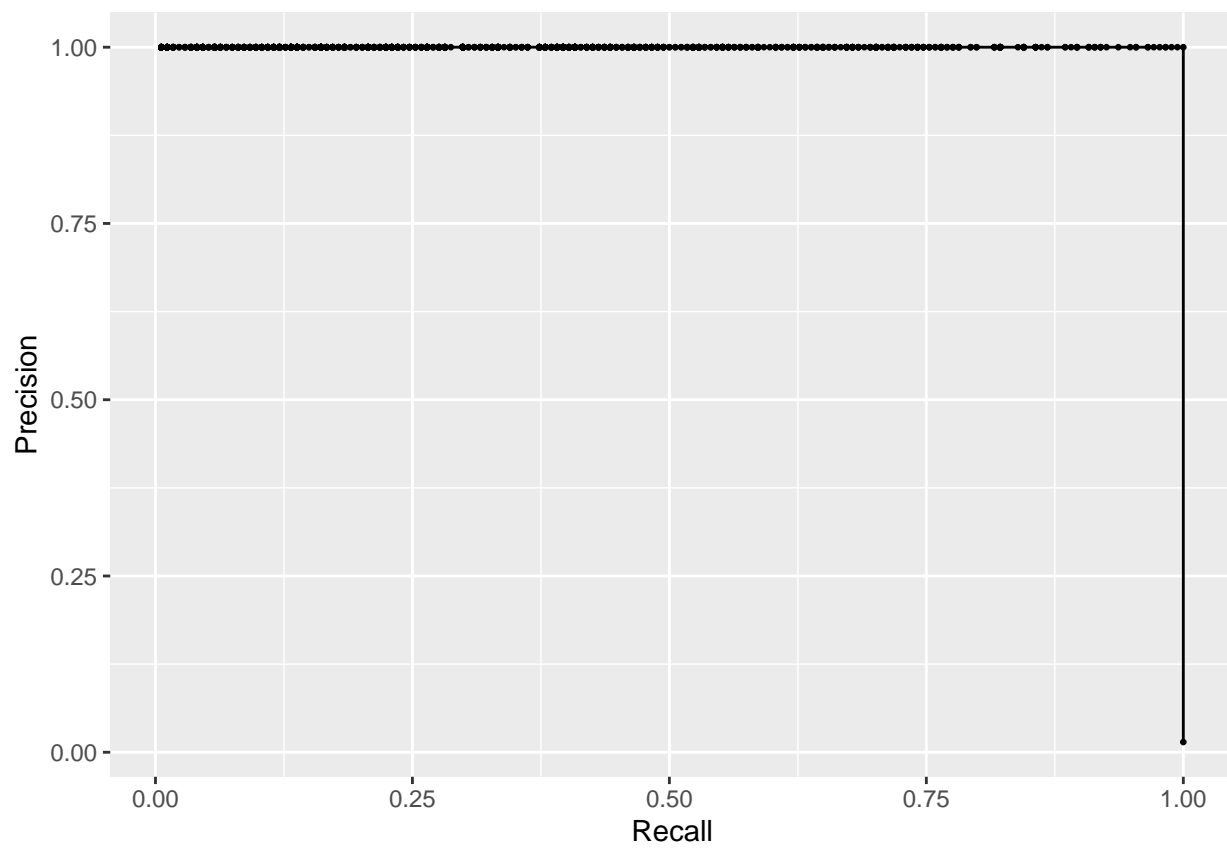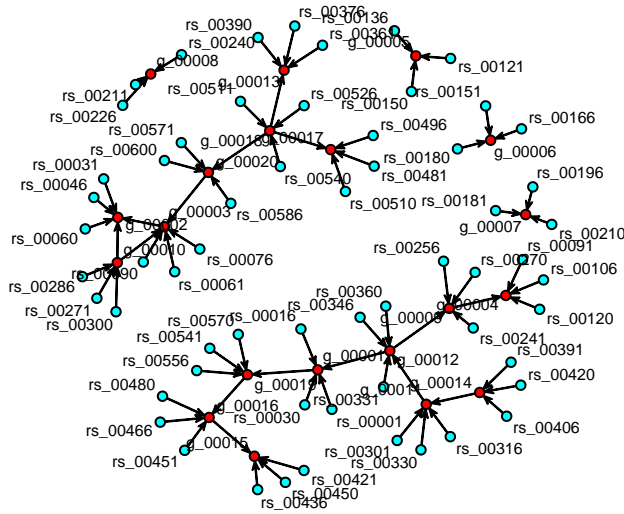
Figure 2: PR curve of trans-eQTL

Figure 3: GRN QTL Network

Estimated GRN and eQTL visualization

```r
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[,
```

Session Information

```r
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
```

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```
> 
> other attached packages:
> [1] Matrix_1.2-14        igraph_1.2.2         ggnetwork_0.5.1
> [4] ggplot2_3.2.1.9000   network_1.13.0.1     ssemQr_0.1.0
> [7] RevoUtilsMath_10.0.0
> 
> loaded via a namespace (and not attached):
>  [1] RevoUtils_10.0.4      tidyselect_0.2.5      xfun_0.4
>  [4] purrr_0.3.0           sna_2.4               lattice_0.20-35
>  [7] colorspace_1.4-0      vctrs_0.2.0.9007      htmltools_0.3.6
> [10] yaml_2.2.0            rlang_0.4.2.9000      pillar_1.4.2.9001
> [13] glue_1.3.0            withr_2.1.2           plyr_1.8.4
> [16] foreach_1.4.4         lifecycle_0.1.0.9000  stringr_1.3.1
> [19] munsell_0.5.0         gtable_0.2.0          mvtnorm_1.0-8
> [22] codetools_0.2-15      coda_0.19-2           evaluate_0.12
> [25] labeling_0.3          knitr_1.21            fssemR_0.1.6
> [28] parallel_3.4.0        rARPACK_0.11-0        Rcpp_1.0.0
> [31] scales_1.1.0.9000     lobstr_1.1.1          farver_2.0.1.9000
> [34] RSpectra_0.12-0       digest_0.6.18         stringi_1.2.4
> [37] dplyr_0.8.99.9000     ggrepel_0.8.0         grid_3.4.0
> [40] tools_3.4.0           magrittr_1.5          glmnet_2.0-16
> [43] tibble_2.99.99.9010   crayon_1.3.4          pkgconfig_2.0.2
> [46] zeallot_0.0.3         MASS_7.3-49           assertthat_0.2.0
> [49] rmarkdown_1.11        iterators_1.0.9       statnet.common_4.1.4
> [52] qtl_1.44-9            R6_2.2.2              compiler_3.4.0
```