explicit

Got a list of genes and you wonder what TFs regulate their expression? EXPLICIT is the right tool to try.

The EXPLICIT approach has been developed to construct a gene expression predictor model for the plant species *Arabidopsis thaliana*. The predictor uses the expression of 1,678 transcription factor (TF) genes to predict the expression of 29,182 non-TF genes. It further enables downstream inference of TF regulators for genes and gene modules functioning in diverse plant pathways. Please check the original paper by Geng *et al.* for more details. The EXPLICIT package presented here enables users to 1. Infer TF regulators for their own gene modules; 2. Draw chord diagrams showing TF-target genes regulation for the modules; 3. Create custom gene expression predictors using their own gene expression data. (*Note: below is an example showing the analysis flow-chart for a gene module involved in vascular system development.*)

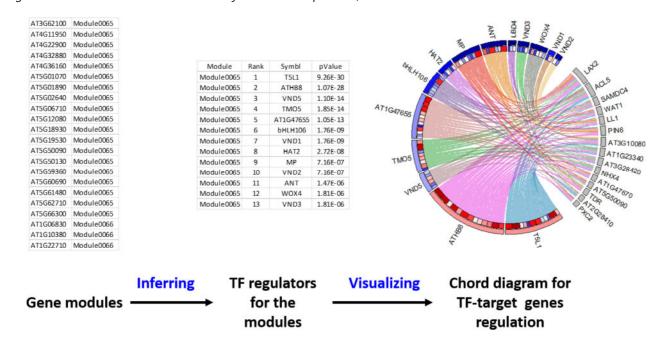


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Install

This package requires Perl, R, and the circlize package in R.

circlize can be installed within an R console via the command:

```
install.packages("circlize")
```

MATLAB is optional. Only required if you want to create your own predictor model using custom expression data.

Once the required software is installed, just download or clone the whole package to a local computer and start using it from the package's home directory.

Usage

1. Infer TF regulators for gene modules

(1). Prepare the module file

The file used to store gene modules information is <code>modules_to_analyze.txt</code>. It is preloaded with 1,085 gene modules identified from a gene co-expression network described in the paper by <code>Geng et al.</code>. The following analysis will proceed with these preloaded modules. On the other hand, you can also edit the file, replacing these modules with your own ones. The file has two tab-separated columns, with the first column being gene ids and the second being module names. For gene ids, only standard Arabidopsis AGI ids are supported. Multiple modules can be analyzed at the same time. Once finish editing, save the file without changing its name.

```
Gene_Name ModuleID
AT1G25360 Module138
AT2G22340 Module138
AT5G75660 Moudle138
AT2G22130 Module139
AT4G12350 Module139
```

(2). Conduct enrichment assay to identify TF regulators for the modules

The Perl script getArabidopsisRegulatorTFs.pl will do the job. It takes the modules from the file modules_to_analyze.txt to conduct enrichment assays to identify potential TF regulators. Results are saved to a file named results.regulator.tfs.txt.

Open a command line window or shell terminal, navigate to the home directory of the EXPLICIT package, and type in the following command:

```
perl getArabidopsisRegulatorTFs.pl
```

The resulted file results.regulator.tfs.txt can be opened and viewed in EXCEL. It lists the potential TF regulators for every input modules. Here is an example:

Module	Rank	TF	Symbl	ModuleSi	Count	CountinG	GenomeS	pValueEn	pValue(bl	Fraction	mean be	TargetAG	TargetSy	rbeta	TargetpValue(-log10 p)
Module0065	1	AT1G68810	T5L1	39	24	527	29182	1.68E-32	9.26E-30	0.615	0.0691	AT5G1953	ACL5/AT2	0.153/0.13	113.4/85.9/65.1/57.9/49.9
Module0065		AT4G32880	ATHB8	39	25	715	29182	3.88E-31	1.07E-28	0.641	0.0943	AT2G2105	LAX2/ACI	0.178/0.15	101.6/86.4/85.1/79.5/59.1
Module0065		3 AT1G62700	VND5	39	10	97	29182	6.00E-17	1.10E-14	0.256	0.0529	AT3G2842	AT3G284	0.076/0.06	26.4/23.8/16.3/14.6/13.9/
Module0065	4	4 AT3G25710	TMO5	39	14	418	29182	1.34E-16	1.85E-14	0.359	0.061	AT5G1953	ACL5/NH	×0.123/0.08	82.9/31.5/29.2/26/25.1/21
Module0065		AT1G47655	AT1G47655	39	16	767	29182	9.55E-16	1.05E-13	0.41	0.0613	AT2G2105	LAX2/SAI	0.102/0.10	61.9/53.5/51.9/43.2/25.3/
Module0065	(AT2G41130	bHLH106	39	9	233	29182	1.94E-11	1.76E-09	0.231	0.0584	AT5G1953	ACL5/AT	0.098/0.06	47.9/16.4/15.3/14.7/14.5/
Module0065		7 AT2G18060	VND1	39	6	43	29182	2.24E-11	1.76E-09	0.154	0.0529	AT3G1008	AT3G100	0.075/0.06	23.1/22.5/18.1/12.7/9.6/9
Module0065		3 AT5G47370	HAT2	39	11	626	29182	3.94E-10	2.72E-08	0.282	0.0473	AT1G7359	PIN1/IAA	30.085/0.08	51.9/36.3/23.3/20.2/20.1/
Module0065		AT1G19850	MP	39	10	666	29182	1.25E-08	7.16E-07	0.256	0.0568	AT2G2105	LAX2/PX	0.121/0.06	59.7/28.9/28.1/19.5/19.4/
Module0065	10	AT4G36160	VND2	39	5	57	29182	1.30E-08	7.16E-07	0.128	0.0478	AT5G5009	AT5G5009	0.063/0.04	19.3/12.6/12.6/10.7/9.1
Module0065	1:	1 AT4G37750	ANT	39	9	537	29182	2.94E-08	1.47E-06	0.231	0.0683	AT2G2105	LAX2/PIN	(0.111/0.11	53.1/49/35.6/16.7/16.2/15
Module0065	12	AT1G46480	WOX4	39	8	390	29182	4.06E-08	1.81E-06	0.205	0.0509	AT5G6148	TDR/PING	0.056/0.06	28.2/21/19.8/19.2/15/9.8/
Module0065	13	AT5G66300	VND3	39	5	72	29182	4.28E-08	1.81E-06	0.128	0.0501	AT5G1953	ACL5/ATS	0.06/0.052	20.2/15.5/11.8/10.6/9.7

2. Draw chord diagrams showing TF-target genes regulation for the modules

The getChordDiagram function can be used to draw chord diagrams for the modules in R. The function extracts the TF-target gene pairs from the file results.regulator.tfs.txt for the input module, and then uses these gene pairs to draw a chord Diagram accordingly. It has four input variables:

```
module - the name of the module
ratio - the relative size of the target gene area occupies

tfnum - the maximum number of TF genes to be included in the diagram

targetnum - the maximum number of target genes to be included in the diagram.
```

Open an R console and change the working directory to the home directory of the EXPLICIT package. Within the R console, type in the following commands:

```
# R code
# Load the scripts that define the getChordDiagram function.
source("Rscripts.R")

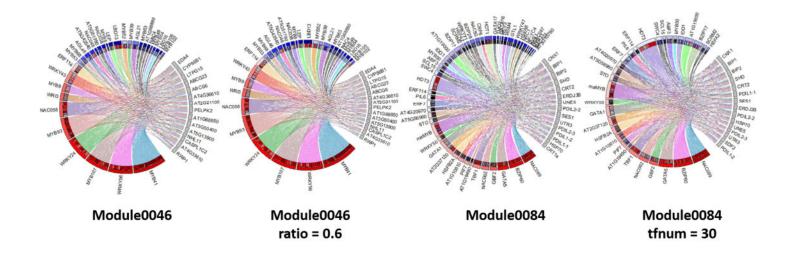
# The function requires the 'circlize' package
library("circlize")

# To draw a chord diagram for Module0105
getChordDiagram( module="Module0105", ratio = 1, tfnum = 50, targetnum = 15)

# Change the relative size of the target gene area
getChordDiagram( module="Module0105", ratio = 0.5, tfnum = 50, targetnum = 15)

# To draw chord diagrams for other modules
getChordDiagram( module="Module0084", ratio = 1, tfnum = 50, targetnum = 15)
getChordDiagram( module="Module0081", ratio = 1, tfnum = 50, targetnum = 15)
getChordDiagram( module="Module0105", ratio = 1, tfnum = 50, targetnum = 15)
```

Here are some output diagrams:



3. Create custom gene expression predictor

We currently only have the gene expression predictor model for *Arabidopsis thaliana*. We are working on predictor models for other species. At the same time, you can also create your own custom gene expression predictor (*Note: a large number of samples are required for training the model*). The MATLAB function **explicit**, as specified within the file **explicit.m**, is used to create the predictor model. The file can be found within the home folder of the package. The function has the following syntax:

```
explicit( TF_expression, TG_expression, TF_name, TG_name)
```

TF_expression: the expression matrix for TF, with samples in rows and genes in columns

TG_expression: the expression matrix for target genes, with samples in rows and genes in columns

TF_name: the names of the TF genes
TG_name: the names of the target genes

Below we describe the detailed procedure to create the Arabidopsis predictor. The procedure can be adapted to analyze other custom gene expression data.

(1). Obtain the Arabidopsis gene expression matrix

Download two matrices At.matrix.demo.hs and At.matrix.full.hs from Figshare (https://figshare.com/s/0c838ad4ef6a764daf53), and place them within the home folder of the EXPLICIT package. We prepared these two matrices by compiling publically available RNA-Seq datasets from NCBI, and used them to train the Arabidopsis predictor. At.matrix.full.hs is a full matrix with 24545 samples, while At.matrix.demo.hs has 5000 randomly selected samples from the full matrix. We recommend to work with the smaller matrix

At.matrix.demon.hs first, as it requires less computational resources. Both matrices are saved in hdf5 file format, with the following data structure. Note that both files also contain an additional matrix with independent samples for validation.

```
At.matrix.demo.h5

--expression_log2cpm (5000 samples [row] X 38194 genes [column])

--gene_name (38194 genes)

--rnaseq_id (5000 samples)

--idx_tf_gene (specifying TF genes used for model construction)

--idx_target_gene (specifying target genes used for model construction)

--independent_samples_for_validation
```

```
-expression_log2cpm (2 samples [row] X 38194 genes [column])
                    (38194 genes)
      gene name
      -sample id
                       (2 samples)
At.matrix.full.h5
                           (24545 samples [row] X 38194 genes [column])
—expression_log2cpm
⊢gene name
                   (38194 genes)
                   (24545 samples)
⊢rnaseq id
─idx_tf_gene
                       (specifying TF genes used for model construction)
                       (specifying target genes used for model construction)
─idx_target_gene
Lindependent_samples_for_validation
   ├──expression_log2cpm (2 samples [row] X 38194 genes [column])
                      (38194 genes)
     --gene name
     --sample_id
                       (2 samples)
```

(2). Create the expression predictor

The following analysis builds a gene expression predictor model using the smaller matrix. The analysis is conducted within a MATLAB console.

```
% MATLAB code
% Navigate to and start within the home directory of the EXPLICIT package.
% Obtain the expression matrix and gene names for from At.matrix.demo.h5.
% The matrix contains 5000 samples (in rows) and 38194 genes (in columns)
mtx_demo = h5read("At.matrix.demo.h5","/expression_log2cpm");
gene name = h5read("At.matrix.demo.h5","/gene name");
% itf specifies which of the 38194 genes are TFs to be used. 1678 TFs are selected in total.
itf = h5read("At.matrix.demo.h5","/idx_tf_gene") == 1;
% itarget specifies which of the 38194 genes are target genes to be used. 29182 target genes are selected
itarget = h5read("At.matrix.demo.h5","/idx_target_gene") == 1;
% Obtain the TF expression matrix, target gene expression matrix
tf_mtx_demo = mtx_demo(:,itf);
target_mtx_demo = mtx_demo(:,itarget);
% Obtain the TF gene names and target gene names
tf_name = gene_name(itf);
target_name = gene_name(itarget);
% Produce the predictor model
mdl_demo = explicit( tf_mtx_demo, target_mtx_demo, tf_name, target_name);
% Take a look into the predictor model
mdl_demo
% The first 5 significant TF-target gene pairs
mdl_demo.SigEdges(1:5,:)
```

The output is:

```
mdl_demo =
 explicit with properties:
                         beta: [1679x29182 double]
                                                      % beta coefficients (1 intercept + 1678 TFs) X 29
                                                      % pValues for the beta coefficiets
                  beta_pvalue: [1679x29182 double]
                      TF_name: [1x1679 string]
                                                      % names for 1 intercept + 1678 TFs
                  Target_name: [1x29182 string]
                                                      % names for 29182 gene
                        NRMSE: 0.0660
                                             % NRMSE for all the training samples
        Correlation_by_sample: [5000x1 double]
                                                  % R of predicted &acutal expression for 5000 samples
   Correlation_by_target_gene: [29182x1 double]
                                                      % R of predicted & actuall exp of each gene acros
                                                      % SST for regression model of every gene
                          SST: [29182x1 double]
                          SSR: [29182x1 double]
                                                      % SSR for regression model of every gene
                          SSE: [29182x1 double]
                                                  % SSE for regression model of every gene
                        Fstat: [29182x1 double]
                                                  % Fstat for regression model of every gene
                      Fpvalue: [29182x1 double]
                                                   % Fpvalue for regression model of every gene
                     SigEdges: [252595x4 table]
                                                   % Significant TF-target gene pairs with pValue <= 0.0
mdl_demo.SigEdges(1:5,:) =
      Gene
                                  beta
                                            beta_pvalue
   "AT1G01020"
                  "AT1G01010"
                                0.1231
                                            1.373e-23
   "AT1G01020"
                  "AT1G15790"
                                 -0.0596
                                            1.074e-06
                                -0.0828
   "AT1G01020"
                 "AT1G25580"
                                            2.755e-06
    "AT1G01020"
                  "AT1G30490"
                                  0.0908
                                            1.053e-06
   "AT1G01020"
                  "AT2G01060"
                                  0.1191
                                            7.535e-06
```

(3). Use the predictor model to predict independent samples

We have generated two independent RNA-Seq datasets from Arabidopsis shoot and root samples. These two datasets were not used in the model training. Below we test how well the predictor model predict these two samples. Note: the order of the gene names within the test samples are the same as those within the demo matrix.

```
% MATLAB code - continued
% Obtain expression matrix for the test samples
test_mtx = h5read("At.matrix.demo.h5","/independent_samples_for_validation/expression_log2cpm");

% test_mtx contains two rows, for 'root' and 'shoot' samples, respetively.
test_sample_id = h5read("At.matrix.demo.h5","/independent_samples_for_validation/sample_id");

test_tf_mtx = test_mtx(:,itf);
actual_target_mtx = test_mtx(:,itarget);

% Predict the expression values for target genes via the formula:
% Predicted expression = [intercept (values of 1) + TF's expression matrix] X beta coefficient matrix
predicted_target_mtx = [ones(size(test_tf_mtx,1),1) test_tf_mtx] * mdl_demo.beta;

% Calculate the correlation between predicted and actual expression values
corr( actual_target_mtx(1,:)', predicted_target_mtx(1,:)') % The correlation for root is 0.9920
corr( actual_target_mtx(2,:)', predicted_target_mtx(2,:)') % The coorelation for shoot is 0.9900

% Calculate NRMSE (Normalized Root Mean Square Error)
% NRMSE for root & shoot samples are 0.0858 & 0.1016
```

```
residual_mtx = predicted_target_mtx - actual_target_mtx;
NRMSE = sqrt(sum(residual_mtx.^2, 2) ./ sum( actual_target_mtx.^2, 2))
```

Note: If you want to use your own RNA-Seq datasets to test the model, make sure the gene names matched in the same order to the gene names of the TF and target gene matrices used above, and the gene expression value should be log2 transformed (log2(CPM + 1)). Alternatively, you can arrange the TFs and target genes of the demo matrix with the same order as your RNA-Seq datasets, and create the gene expression predictor accordingly.

(4). Investigate how the number of training samples affects the predictor power

The number of training samples affects the predictor's predicting power. The function <code>explicit_eosn</code>, standing for effect of sample number, investigates such effects. Its inputs are <code>(TF_expression, Target_expression, TestSampleNum)</code>, with <code>TestSampleNum</code> being the number of samples randomly selected and hold out as test samples.

```
% MATLAB code - continued
% Hold out 500 samples as test samples
mdl_eosn = explicit_eosn( tf_mtx_demo, target_mtx_demo, 500)
mdl_eosn
mdl_eosn.stat
```

The output is:

Run	TrainingSampleNum	R_training	NRMSE_training	R_test	NRMSE_test	
1	1700	0.99995	0.0071425	0.68378	0.931	
2	1725	0.99988	0.010676	0.79395	0.63758	
3	1750	0.99983	0.013001	0.82836	0.54658	
4	1775	0.99975	0.015839	0.86977	0.43926	
5	1800	0.99969	0.017487	0.88968	0.38962	
6	1850	0.99958	0.020327	0.91018	0.34773	
7	1900	0.99943	0.023749	0.92621	0.30313	
8	1950	0.9993	0.026351	0.93624	0.27771	
9	2000	0.9992	0.028108	0.94274	0.26096	
10	2100	0.99897	0.031836	0.95118	0.2338	
11	2200	0.99877	0.034816	0.95963	0.20954	
12	2300	0.99854	0.037856	0.96267	0.20082	
13	2400	0.99838	0.039831	0.96647	0.18906	
14	2500	0.99819	0.042092	0.96992	0.17783	
15	3000	0.99737	0.05082	0.97769	0.15087	
16	3500	0.99679	0.056046	0.981	0.13833	
17	4000	0.99629	0.060238	0.98307	0.13	
18	4500	0.99587	0.06356	0.98441	0.12439	

Eighteen predictor models were built with between 1700 and 4500 training samples, and the predicting accuracy on test samples (R_test) increased along with the number of training samples.

(5). Perform K-fold Cross-Validation

K-fold Cross-Validation can be also used to test the predictor's performance. The function <code>explicit_kfcv</code> does the job. Its inputs are (TF_expression, Target_expression, tf_name, target_name, repeats, folds), with repeats and folds being the number of repeats and the folds for the analysis.

```
% MATLAB code - continued
% Perform 5 repeats of 10-fold Cross-Validation
mdl_kfcv = explicit_kfcv(tf_mtx_demo, target_mtx_demo, tf_name, target_name, 5, 10)
mdl_kfcv
mdl_kfcv.CV_Stat
mdl_kfcv.AllEdges(1:5,:)
```

The output is:

```
mdl_kfcv =
  explicit_kfcv with properties:
                  Total_repeats: 5
                    Fold_number: 10
    Correlation_of_target_gene: [29182x50 double]
                                                       % R of target genes in test samples in all 50 CV runs
              Target_gene_name: {29182x1 cell}
                                                       % The statistics for each coefficient across 50 CV ru
                       AllEdges: [48996578x9 table]
                        CV_Stat: [50x6 table]
                                                       % R and NRMSE for training and test samples in each C
mdl_kfcv.CV_Stat =
                                                                          R_test
   Repeat
             Fold_No
                         NRMSE_training
                                            NRMSE_test
                                                           R_training
      1
                  1
                             0.063782
                                              0.12305
                                                             0.99584
                                                                           0.98481
      1
                  2
                             0.063719
                                              0.12509
                                                             0.99585
                                                                           0.98418
      1
                  3
                                                                           0.98232
                             0.063326
                                              0.13161
                                                              0.9959
                  4
                                                                           0.98209
      1
                             0.063505
                                              0.13506
                                                             0.99588
      1
                  5
                                              0.14025
                                                             0.99592
                                                                           0.98067
                             0.063122
      1
                  6
                             0.063771
                                              0.11977
                                                             0.99584
                                                                           0.98526
                  7
      1
                                              0.13044
                                                             0.99591
                                                                           0.98294
                             0.063166
      1
                  8
                             0.063427
                                               0.1368
                                                             0.99589
                                                                           0.98111
                 9
      1
                             0.063389
                                              0.13608
                                                             0.99589
                                                                           0.98168
      1
                10
                              0.06349
                                              0.13053
                                                             0.99588
                                                                           0.98278
      2
                  1
                             0.063595
                                              0.13268
                                                             0.99586
                                                                           0.98234
      2
                  2
                             0.063495
                                                             0.99587
                                                                           0.98335
                                              0.12829
      2
                  3
                             0.063617
                                              0.12701
                                                             0.99586
                                                                           0.98347
      2
                  4
                              0.06349
                                              0.12768
                                                             0.99588
                                                                           0.98357
      2
                  5
                              0.06351
                                              0.13197
                                                             0.99587
                                                                           0.98255
mdl_kfcv.AllEdges(1:5,:) =
     Gene
                                   beta
                                             beta pvalue
                                                             CV_beta_mean
                                                                              CV_beta_std
                                                                                              beta bias
                                                                                                            bet
    "AT1G01020"
                                    0.58075
                                                                   0.58822
                                                                                                 0.00747
                    "intercept"
                                                   0.02262
                                                                                  0.13633
    "AT1G01020"
                    "AT1G01010"
                                    0.12307
                                                1.373e-23
                                                                   0.12226
                                                                                  0.01281
                                                                                                 -0.00081
    "AT1G01020"
                    "AT1G01030"
                                    0.01859
                                                   0.08915
                                                                   0.01981
                                                                                  0.00563
                                                                                                 0.00122
    "AT1G01020"
                    "AT1G01060"
                                    -0.0292
                                                 0.001083
                                                                  -0.02862
                                                                                  0.00599
                                                                                                 0.00058
    "AT1G01020"
                    "AT1G01250"
                                    0.02899
                                                   0.00919
                                                                   0.02742
                                                                                  0.00629
                                                                                                 -0.00157
```

mdl_kfcv.AllEdges can be used to check if any of the coefficient is stable or not across the CV runs.

(6). Perform Cross-Validation on independent samples

The function <code>explicit_cv</code> can be used to conduct Cross-Validation. Its inputs are <code>(Training_TF_expression, Training_traget_expression, Test_TF_expression, Test_target_expression, Test_sample_ids)</code>. The function uses the Training TF and target expression matrices to build the predictor model, and then test the model on the Test samples. It provides a covenient way to generate and test different predictor models.

```
% MATLAB code - continued

test_target_mtx = test_mtx(:,itarget);

% Use all 5000 samples in the demo matrix to build the preidctor model,
% and test on the shoot and root RNA-Seq samples.
mdl_cv_5000 = explicit_cv( tf_mtx_demo, target_mtx_demo, test_tf_mtx, test_target_mtx, test_sample_id)

% Use only 4000, 3000, or 2000 samples to build the predictor model
mdl_cv_4000 = explicit_cv( tf_mtx_demo(1:4000,:), target_mtx_demo(1:4000,:), test_tf_mtx, test_target_mtx
mdl_cv_3000 = explicit_cv( tf_mtx_demo(1:3000,:), target_mtx_demo(1:3000,:), test_tf_mtx, test_target_mtx
mdl_cv_2000 = explicit_cv( tf_mtx_demo(1:2000,:), target_mtx_demo(1:2000,:), test_tf_mtx, test_target_mtx
mdl_cv_5000
mdl_cv_5000.Test_Sample_Stat
```

The output is:

When using 5000, 4000, 3000, or 2000 samples to train the predictor model, the mean correlation for test samples are 0.9910, 0.9891, 0.9841, 0.9572, respectively.

(7). Use the full matrix to perform the analysis

Next we will analyze the full matrix. *Note: Since the matrix is large, it requires a large amount of computational resource. It is recommended to have at least 80G memory available.*

```
% MATLAB code
% clear all previous variables to free memory
clearvars;
% Step A. Create the predictor
mtx full = h5read("At.matrix.full.h5","/expression log2cpm");
gene_name = h5read("At.matrix.full.h5","/gene_name");
itf = h5read("At.matrix.full.h5","/idx tf gene") == 1;
itarget = h5read("At.matrix.full.h5","/idx_target_gene") == 1;
tf mtx full = mtx full(:,itf);
target_mtx_full = mtx_full(:,itarget);
tf_name = gene_name(itf);
target_name = gene_name(itarget);
% This produces the predictor model.
mdl_full = explicit( tf_mtx_full, target_mtx_full, tf_name, target_name);
mdl_full
% The predictor has 3298936 SigEdges (TF-target gene pairs) with pValue <= 0.00001
% Next the SigEdges with pValue <= 1e-9 are extracted and saved to a file named "Arabidopsis.SigEdges.1e-
% This file is the same as the file "At.SigEdges.txt" within the data directory.
% There are 980736 SigEdges with pValue <= 1e-9.
% These SigEdges are also the same SigEdges reported in the paper by Geng et al.
i = mdl_full.SigEdges{:,4} <= 1e-9 ;</pre>
sum(i)
writetable( mdl_full.SigEdges(i,:), "Arabidopsis.SigEdges.1e-9.txt", "Delimiter", "tab")
% Step B. Investigate how the number of training samples affects the predictor power
mdl_eosn = explicit_eosn( tf_mtx_full, target_mtx_full, 3000)
mdl eosn
mdl eosn.stat
% Step C. K-fold Cross-Validation
mdl_kfcv = explicit_kfcv(tf_mtx_full, target_mtx_full, tf_name, target_name, 5, 10)
mdl kfcv
mdl_kfcv.CV_Stat
mdl_kfcv.AllEdges(1:5,:)
% Step D. Cross-Validation on independent samples
test_mtx = h5read("At.matrix.full.h5","/independent_samples_for_validation/expression_log2cpm");
test_sample_id = h5read("At.matrix.full.h5","/independent_samples_for_validation/sample_id");
test_tf_mtx = test_mtx(:,itf);
test_target_mtx = test_mtx(:,itarget);
mdl_cv_full = explicit_cv( tf_mtx_full, target_mtx_full, test_tf_mtx, test_target_mtx, test_sample_id)
mdl cv full
mdl_cv_full.Test_Sample_Stat
```

The output is:

The mean correlation for the test samples is 0.9934 for the full model, which is better than the model constructed with 5000 samples within the demo matrix.

Reference

Will update soon.