

FIGS User's MANUAL

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1.0 GENERAL INFORMATION

1.1 System Overview

Fuzzy inference of gene sets (FIGS) is a Matlab-based standalone executable package that uses dendritic cell and A549 epithelial cell influenza response to represent data driven fuzzy gene-sets. This interactive graphic user interface (GUI) package comes with several control parameters to probe fuzzy gene-sets where you can also perform enrichment analysis by providing your own gene set. The results of overlapping gene-sets are presented as circular graph that can be inspected interactively.

1.2 Authorized Use Permission

FIGS is developed solely for the research purpose to benefit immunologist and broader bioinformatics community. FIGS is freely available for the personal use. However, unauthorized or commercial redistribution of FIGS is highly prohibited.

The use of FIGS package is subject to the following conditions:

- (1) The package and portions thereof may not be sold. Users may modify the software for their own use, but may not redistribute any version of the package other than the original version without the express permission of the authors.
- (2) This package is provided on an "as is" basis. The authors in no way warrant either this package or results it may produce.
- (3) The authors are under no obligation to provide any services by way of maintenance, updates or corrections for this package.
- (4) Reports or publications resulting from use of this package must contain an acknowledgment in the form commonly used in academic research.

By downloading this package, you agree to the above conditions.

1.3 Points of Contact

For further information regarding development of FIGS, assistance in using FIGS or potential collaborative opportunities please contact:

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1.4 Citing FIGS

Thank you for using FIGS. Please cite the FIGS package as:

- Atif Khan, Dejan Katanic and Juilee Thakar, “FIGS: Fuzzy Inference of Gene-Sets: A data driven clustering approach”, PLOS Computational Biology, vol. XX, pp. YY, ZZ. (To be updated later)

FIGS is an advanced tool developed subsequently after PathCellNet that can be accessed at <http://www.bio-networks.com/>. Please cite PathCellNet as:

- Dejan Katanic, Atif Khan and Juilee Thakar. "PathCellNet: Cell-type specific pathogen-response network explorer." Journal of Immunological Methods (2016).

1.5 Acronyms and Abbreviations

FIGS: Fuzzy inference of gene-sets

PathCellNet: Pathogen specific cell type network

DC: Dendritic cells

EC: Epithelial cells

FCM: Fuzzy c-means clustering

ISGs: Interferon stimulated genes

KEGG: Kyoto encyclopedia of genes and genomes

U: Unified distance matrix

MV: fuzzy membership value

GUI: Graphic user interface

2.0 INSTALLATION AND SYSTEM REQUIREMENTS

FIGS is a computational package that allows user to identify groups of gene signatures in human monocyte derived dendritic cell (DC) and A549 epithelial cells (EC) responsive to influenza infection.

2.1 System Requirements

FIGS is developed in Matlab R2016a environment and deployed as installable package. FIGS package does not explicitly require Matlab but it requires 'Matlab Runtime' during the installation process (in case you haven't installed it previously).

The 'Matlab Runtime' is a freely available standalone set of shared libraries that enables the execution of compiled Matlab applications or components on computers that do not have Matlab installed.

2.2 Installation Procedure

FIGS can be downloaded from <https://github.com/Thakar-Lab/FIGS>

Please make sure you downloaded FIGS.exe file (~20 Mb) from GitHub. Double click FIGS.exe to install FIGS package on the desired directory.

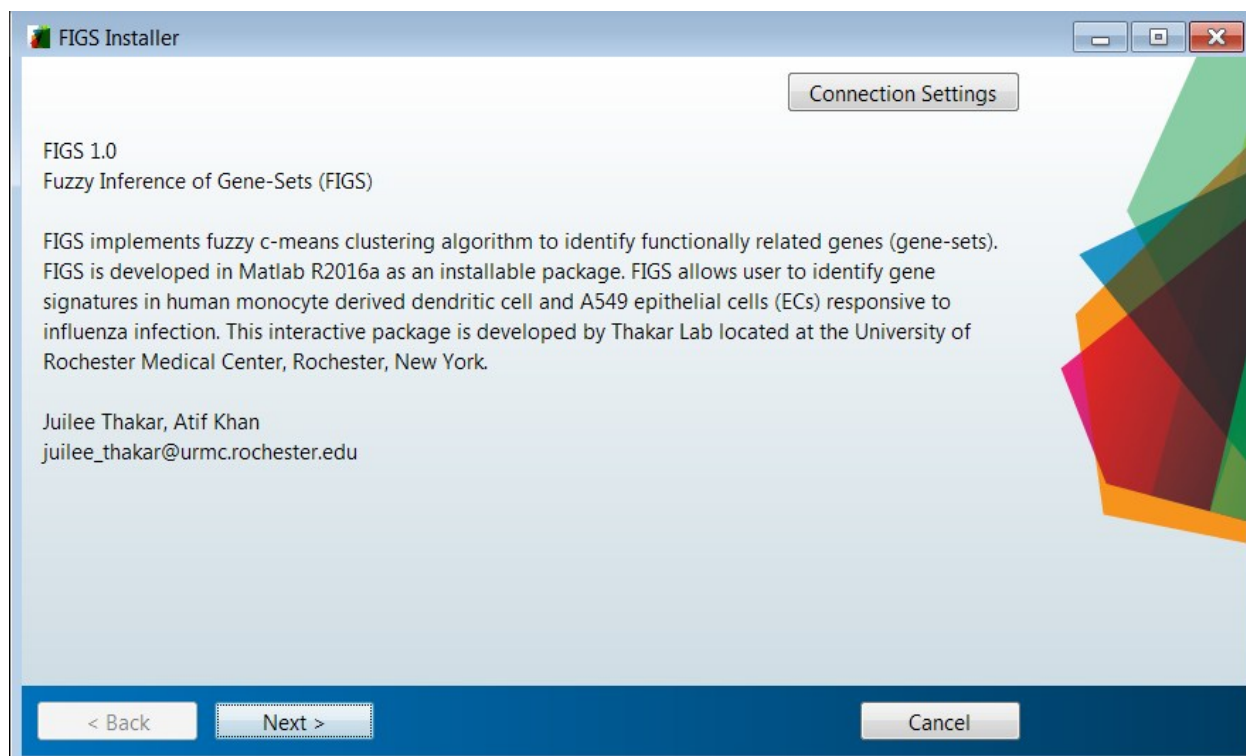


Figure 1: Installation of FIGS Package

If the FIGS installer finds the appropriate version of 'Matlab Runtime' already installed on your PC, the following information will be displayed (Figure 2) and you will no longer be required to install it again.



Figure 2: Detection of Previously Installed Matlab Runtime

In case the 'Matlab Runtime' is not found on your PC, the following information will be displayed (Figure 3). For the ease of use, 'Matlab Runtime' compiler installation is packaged with FIGS.exe. You will be automatically redirected to the Matlab website for downloading and installation of Matlab compiler (Figure 4).

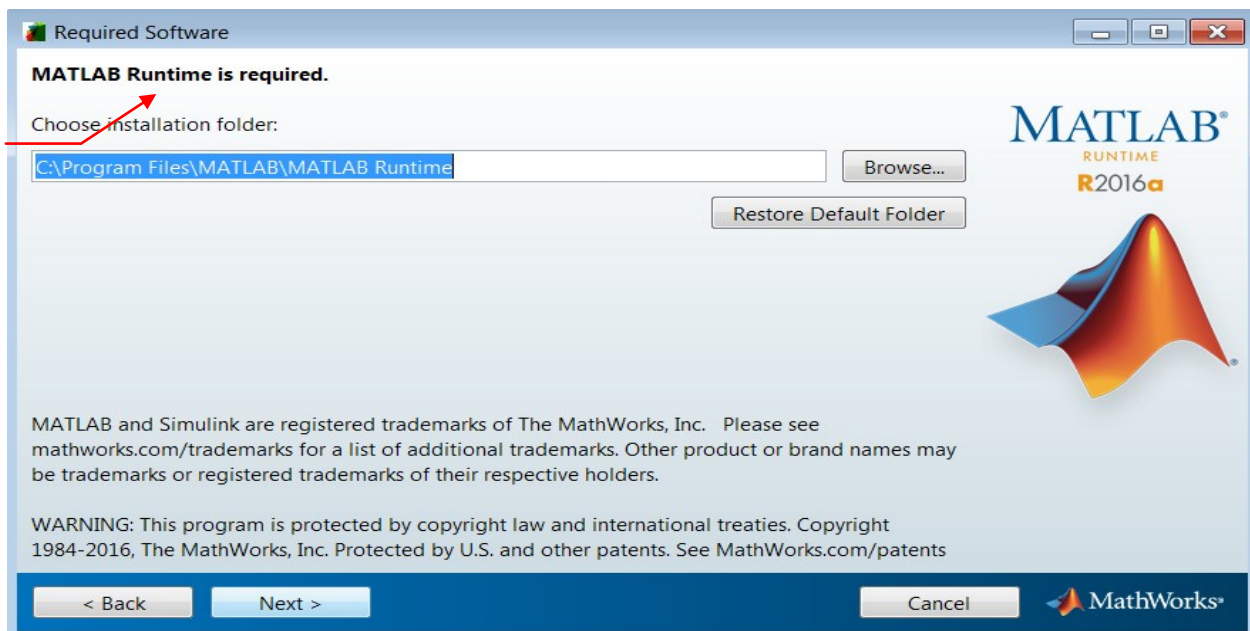


Figure 3: Matlab Runtime Installation Requirement

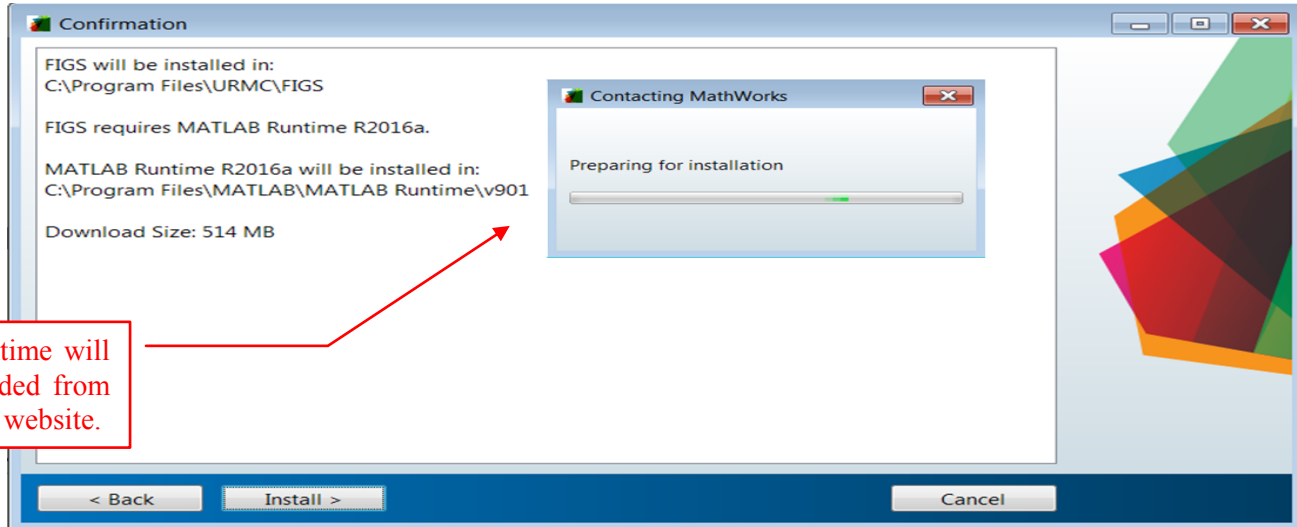


Figure 4: Automatic Downloading of Matlab Runtime

Please beware that Matlab Runtime (size ~500 Mb) will be downloaded from Matlab website (www.MathWorks.com). Downloading and installation (Figure 5) might take some time depending on your connection and internet speed.

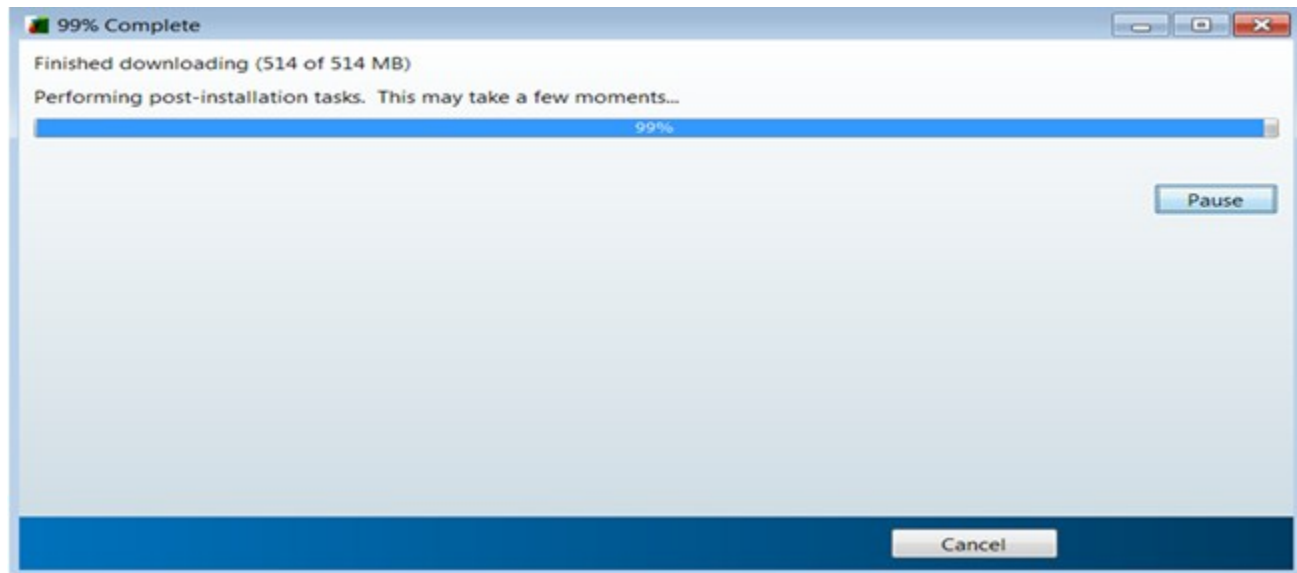


Figure 5: Automatic Installation of Matlab Runtime

2.3 Getting Started

Once the installation is finished, FIGS package can be accessed by running FIGS application from the program list (in case you have not created a desktop shortcut).

3.0 MAIN SYSTEM MENU

This section provides a general overview of the FIGS package with the help of screen shots.

3.1 Graphic User Interface

Run FIGS from the program list (in case you have not created a desktop shortcut). The main menu will appear with several control parameters as shown and described in figure 6.

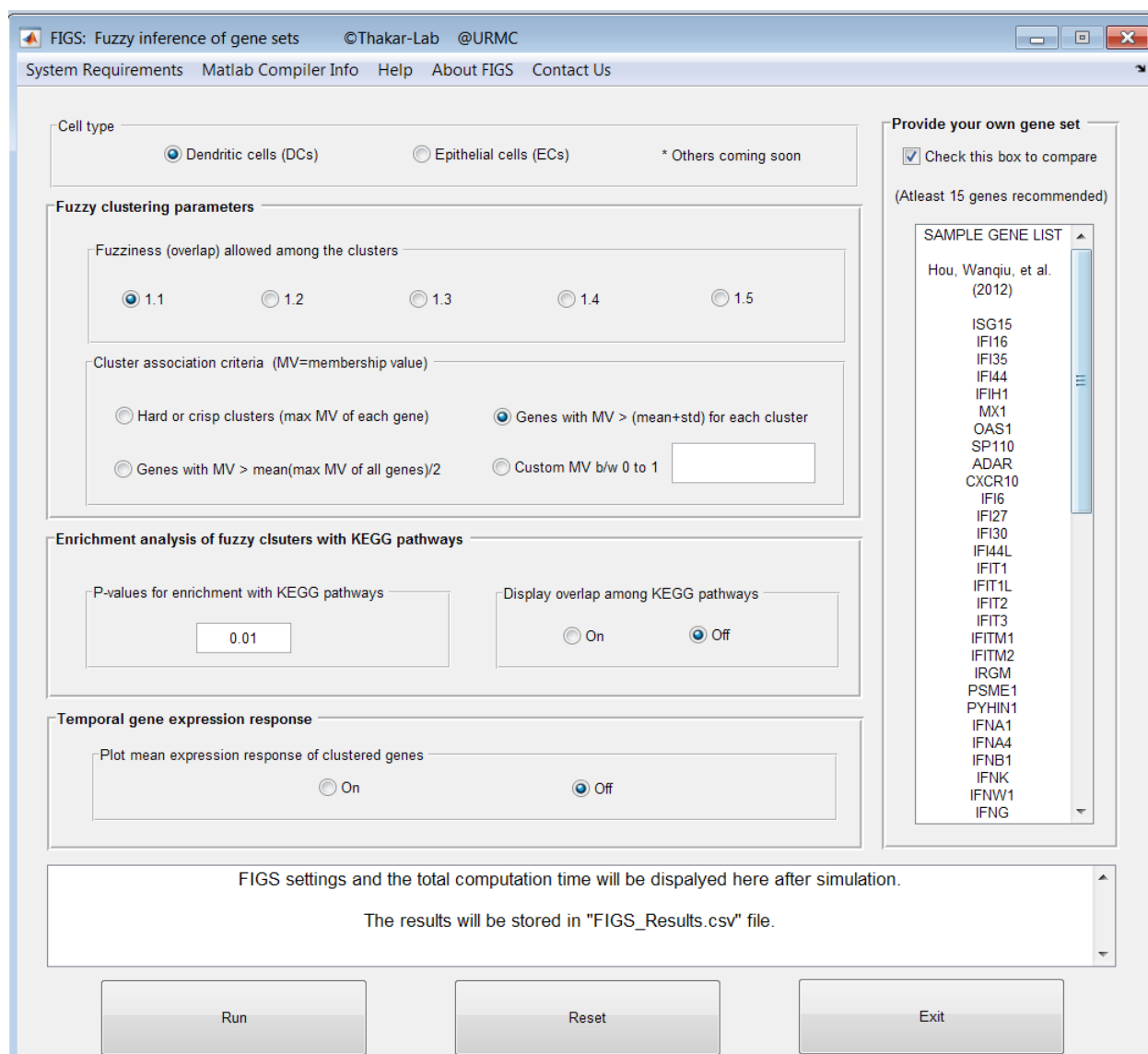


Figure 6: Main GUI of FIGS Package

3.2 Menu Tabs

The main menu of FIGS that has several navigation tabs and menu bars. The description of tabs and the menu bars (figure 7) are self-explanatory.

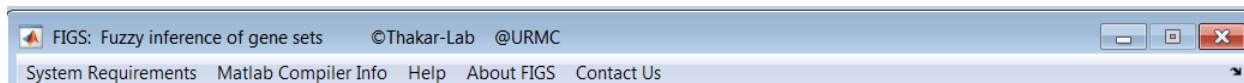


Figure 7: Main Menu Tabs

3.3 Cell Type Selection

Currently, FIGS package database includes Dendritic Cells (DCs) and Epithelial Cells (ECs). The results of FCM clustering for these datasets are stored in database to save computational time and facilitate quick retrieval. In future, more cell types will be added to the database and FIGS package will be updated accordingly.

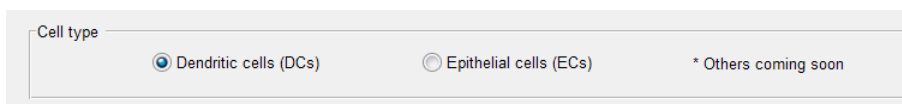
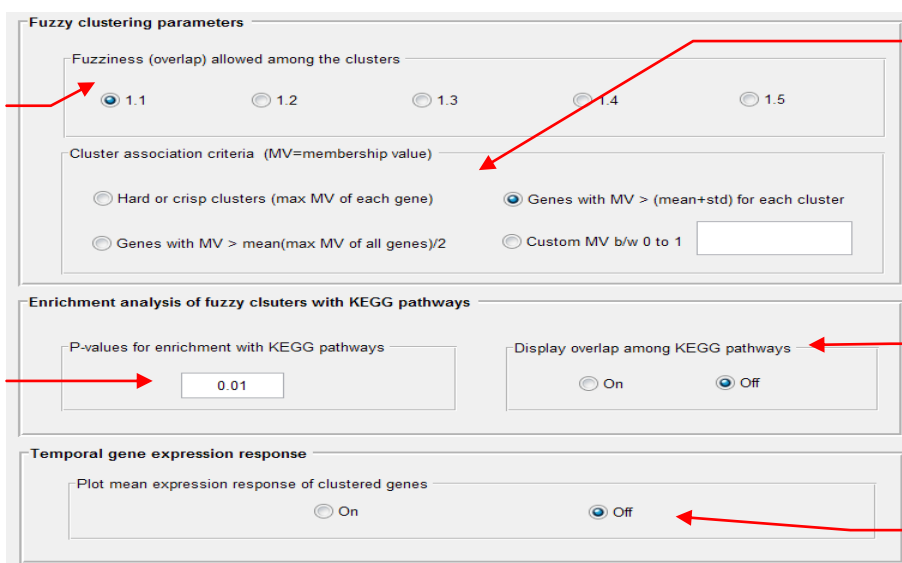


Figure 8: Cell Type Selection Tabs

3.4 Panel of Controllable Parameters

FIGS package comes with several user defined control parameters. We recommend using the default parameters but for the exploratory purposes, parameters can be modified depending on your requirement.



The extent of overlap allowed between the clusters. (A high value means more overlap).

Four different criteria for associating genes to the clusters, 1: Hard clusters 2: The distribution based assignment. 3: Mean-Max ($\sum_{i=1}^n \max(U_i)/2n$) and 4. User defined threshold.

Set p-value cutoff for the enrichment of FCM gene-sets with 44 immunological relevant KEGG pathways and Interferon stimulated genes.

Provides an additional output to represent overlap among ISGs and KEGG pathways.

Provides an additional output plot to represent temporal expression of the clustered genes.

Figure 9: Controllable Parameters of FIGS Package

3.5 Upload User Gene-Sets

There is an option to provide your own gene-sets for enrichment with FCM produced gene-sets. Gene names can be manually entered or can be copy-pasted in the panel shown below (Figure 10). To do the enrichment of your own gene-sets, please check the box “Check this box to compare”.

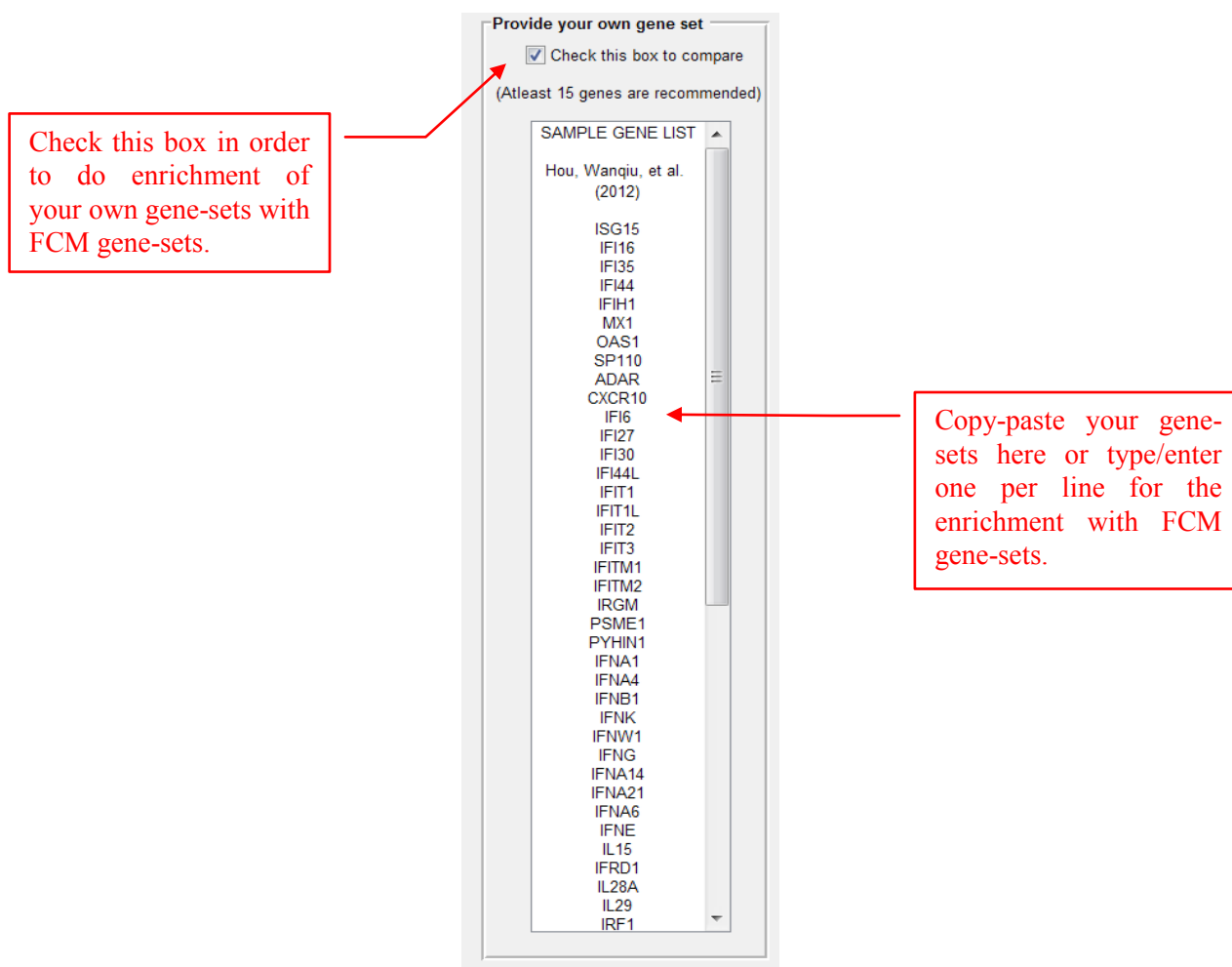


Figure 10: User Provided Gene-Sets for Enrichment with FCM Gene-Sets

3.6 Run, Reset and Exit

Pressing the run tab will start computation and exit tab will quit the package. Pressing reset tab will clear the setting of all the parameters to the default state.

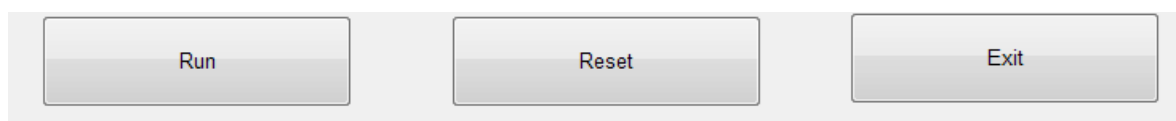


Figure 11: Control Tabs for Computation

3.7 Error Dialogs

The package will show an error dialog if the cell type, cluster association criteria and/or fuzziness values are not selected. Additionally, there will be an error message if the value of the user provided membership value threshold is not between 0 and 1.

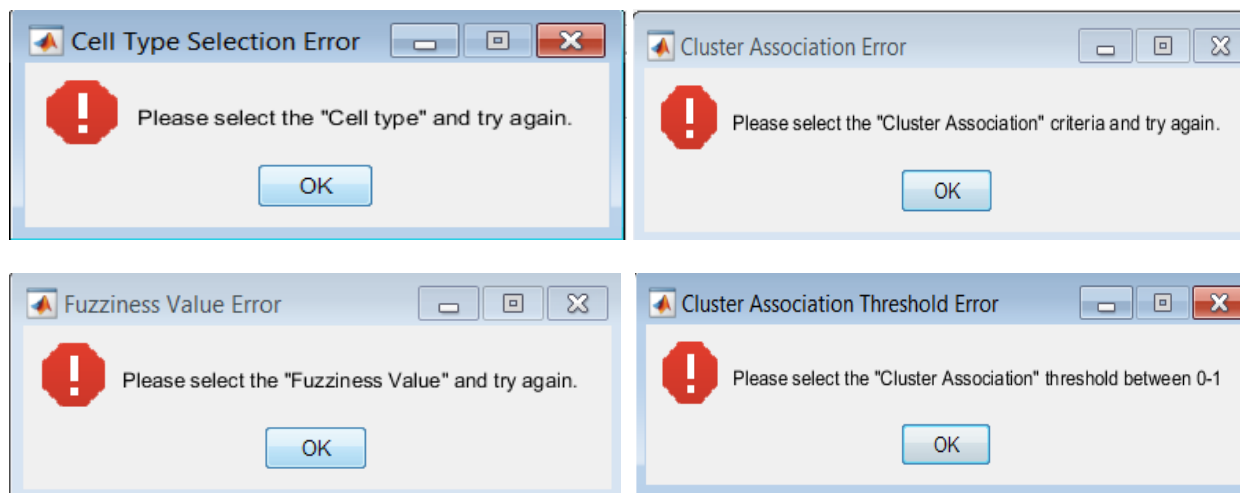


Figure 12: Error Dialogs for FIGS Parameter Settings

3.8 Progress Bars

The package computes output in three steps as shown in Figure 13. The progress at each step will be shown by the green color progress bar.

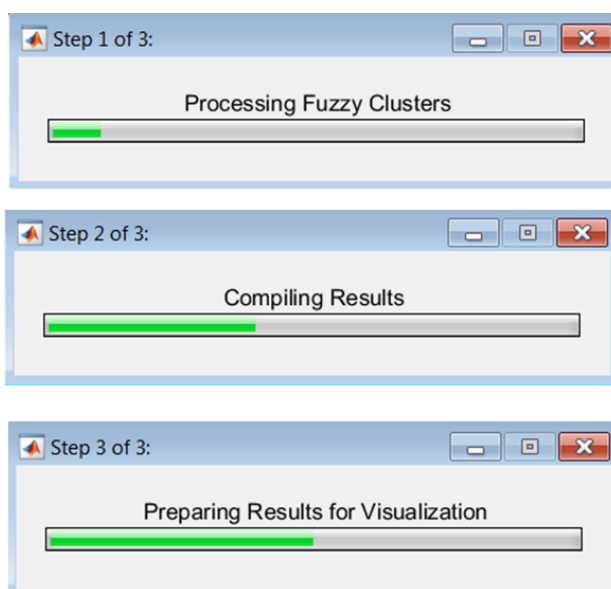


Figure 13: Automatic Installation of Matlab Runtime

4.0 USING THE SYSTEM

This section provides a descriptive usage of the FIGS package.

4.1 Fuzzy Gene-Sets

The results of FCM gene-sets are displayed in tabular as well as interactive circular graphs. Figure 14 shows the composition of FCM gene-sets and their enrichment with KEGG pathways (where red color shows significant overlap based on user selected p-value).

FIGS Genesets

Thakar-Lab @ UMMC

KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION

KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY

KEGG_NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY

KEGG_RIG_LIKE_RECEPTOR_SIGNALING_PATHWAY

KEGG_CYTOSOLIC_DNA_SENSING_PATHWAY

KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY

KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY

KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY

KEGG_FC_EPSILON_RL_SIGNALING_PATHWAY

KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS

KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_ISCA_PRODUCTION

INTERFERON_STIMULATED_GENES_SCHOGGINS

C35

C36

C37

C38

C39

C40

C41

C42

C43

C44

C45

C46

C47

C48

C49

0.15866

0.20181

0.094257

0.70654

0.61489

0.6358

0.085645

0.16337

0.67694

0.79738

0.47505

0.025991

0.25362

0.69698

0.072629

0.22917

0.02059

0.00040081

0.78873

0.70179

0.72217

0.46568

0.0017766

0.76134

0.58434

1.3193e-05

0.0029213

0.12451

0.060583

0.60252

0.11124

0.1424

0.055336

0.6247

0.53063

0.55398

0.32641

9.7232e-05

0.59473

0.12795

0.091665

0.0126

0.04537

0.0022174

0.13218

0.38234

0.0001937

0.0006741

0.55792

0.47023

0.48956

0.28043

0.064969

0.52871

0.65453

3.0293e-06

0.0053884

0.13621

0.042237

0.28563

0.37231

0.015825

0.031968

0.5457

0.12218

0.13394

0.27247

0.00021753

0.15596

0.26676

4.5863e-05

0.0056454

0.46885

0.038732

0.27241

0.6547

0.0071803

0.2137

0.83495

0.75392

0.7733

0.51631

4.687e-06

0.48845

0.19548

0.066355

0.23175

0.4192

0.5176

0.027948

0.096069

0.0028803

0.000779

0.55827

0.15076

0.52295

0.30379

0.081685

0.53226

0.68946

0.37651

0.0009880

0.00941

0.21232

0.32509

0.041814

0.11963

0.10918

0.36968

0.26542

0.65961

0.28043

0.44962

0.69297

0.50087

0.030004

0.70805

0.2778

0.35761

0.22807

0.042237

0.22908

0.11434

0.14275

0.27322

0.6672

0.41633

0.1946

0.34235

0.24131

0.1525

0.0074425

0.65841

0.72762

0.51993

0.0268

0.53587

0.26103

0.30072

0.21103

0.60146

0.3625

0.72737

0.26897

0.41932

0.019039

0.019078

0.59267

0.66292

0.1744

0.36213

0.093781

0.029165

0.53314

0.44725

0.46609

0.26443

0.58792

0.50441

0.25373

0.32994

0.51175

0.48809

0.52374

0.63465

0.58067

0.01719

0.37707

0.17513

0.68208

0.33627

0.44768

0.50455

0.38712

0.28868

0.17782

0.15466

0.69403

0.76162

0.29639

0.29748

0.0073219

0.097951

0.45019

0.37222

0.36909

0.21429

0.0042628

0.42379

0.54108

0.0034739

0.10513

0.38191

0.11122

0.54648

0.87416

5.3629e-29

0.088163

0.94137

0.68872

0.87527

0.70263

5.1182e-05

0.91745

0.99967

1.7225e-60

0.023966

0.95646

0.35888

0.95783

Enrichment (P-Value) of FIGS gene-sets in user-defined genes

Total genes found in fuzzy clusters

50207079

0.614315

0.523609

0.543834

0.318949

0.0223177

0.584004

0.710774

3.9640e-16

0.00167989

0.53527

0.0620247

0.351105

1

C26

C27

C28

C29

C30

C31

C32

C33

C34

C35

C36

C37

C38

C39

C40

C41

C42

C43

C44

C45

C46

C47

C48

C49

ZORF28

C10RF77

FCER1

DMIT1L

LOC1

RAPH1

HMB5

COG2

C3ORF34

TPMT

DDI60

TMEM206

HSD17B12

ADIPOR1

HIF1

HSD17B7

LOC728830

CCNC

PH6

MT2A

LOC728501

LOC646483

LOC651202

PRDM14

11

TM2P2

FCER1

LOC100128104

LOC100128104

C3ORF156

C12ORF47

BBD2

KCNH6

TACC1

UBE2L6

TCF12

COMMD1

CNPY2

DBNDD2

CRCP

LTA

CYB5B4

EXOSC7

IFTM2

KULH28

LOC644039

LOC389787

VRK3

3

SCALES

INCB02

FLVCR2

CDKRAP1

CDIC

RAE1

RIF4

ZMYND19

HSPC289

TRPV2

LOC10013381

NYC

NOUAF1

C14ORF156

DUSP22

LOC729603

SORBS1

RIASE1

CDIC23

POGFR

THFAP8L3

HSD1A

FTHL8

TBP

4

NO6

SMAD4

LSM14A

PGL1

PGK1

MAP3K11

LOC100133484

C4ORF156

TGFBI

SP110

TPD52L2

SUPT4H1

ERH

NHP2

BLZF1

COL20

LOC100131100

LOC10013221

FTM3

DUSP6

BTIF3

LOC646785

PAK2A

5

40

OTUD4

CD1E

WDR6

ACOX3

HMOCS1

PMM1

MTMR12

SEMA3E

TORG1

MCB

TCPI

CO15A

GLTSCR2

MCCE

MCMB

PM1

LOC387791

PMPD

USP41

NFKB1

SF3B14

LOC1001231

YPF6

6

72

ADAM17

LOC650215

TTG16

COQ10B

MEIO30

DCTPP1

PREX1

CO3E1

TKT

EPF2AK2

THEM2

ARPC2

SULT1A4

PTPMT1

LOC100133ESAT1

ARPC5

CNTM8

MI2

LGAM

RPSA11

PTMA

ZNF142

7

L1

BAGL1

HACL1

C2ORF29

LOC2ORF51

PURB

C7ORF49

LOC731314

ZNF682

TMED9

LBA1

TBPL1

LOC653225

C14ORF112

LOC10013172

ZNF549

LOC387763

LOC1001316

GPD1L

C19ORF66

SNX16

POLE4

LOC100131

REBM14

8

B1

PPTC7

UBE4B

MTF2

BCAP31

ARNTL

CLEC4A

ZNF275

LOC1001267

TMEM101

SERPINC1

CD163

RAB31

DUSP23

MRPS15

LOC731542

COL3L1

PABPN1

SLC3A3R1

IL15RA

PLRA

OSTC

LOC388621

FAM105E

9

R3

ZC3H4

IK

DEIR

C16ORF24

MED19

ZNF382

RRS1

CCDC125

NGRN

OAS3

TFOP2

FUCA2

EIF3E

TPM1

MG28336

CO89

LOC728823

PTGFRN

INTS3

GTZE1

PPA2

FLJ43681

RAVIGAP

10

P

PTGERA

PDHB

GSA2

DNAJB11

PAPSS2

PRAM1

FKBP4

LOC729090

TRIM4

DTXL

NOUAF3

PSMB4

ZNF428

GLR15

LRR337B2

COL2

C10RF43

ARAP3

HES4

EWSR1

HCF1R1

LGAL3

CTN15

11

7

SAP9L

LOC654191

MAVBA

FAM174A

RAP1GAP

LOC728431

COX15

LOC1001253

MEU1

LOC100132E1

FRSF14

LOC728200

C6ORF108

REI102

LOC644250

MGCI0997

LOC729992

MFSD6

OAS2

LRRRC2

LOC646688

LOC1001257

YINC1H

12

IRIN2

PSCDBP

FADS1

LARS

LOC100130

FRBS

MAP7

FARSA

LOC730313

TMEM19

DYLL1T1

SASH1

SOD1

LOC844877

C17ORF91

ZNF738

SOO2

COX8B1

EBNA1BP2

ISG15

PPP1R10

LSM5

FTH1

FBI011

13

B

ZNF22

ANAPC5

HEATR2

LDHA

PAFAH1B1

CEHPB

KIAA0319L

ARL16

NOSP

CCNA1

MTX

PAPOLA

ATP50

ZNF511

CREB1

HST2H2A4

LOC644131

C10ORF54

APOL3

YEATS2

LOC644863

LOC100132ESL1

C142

14

C41A2

RAPGEF2

LTV1

DDI18

OXB

PTGER2

CEGR5

WDFY2

LOC36586

TBIAS1

IFH1

INSIG2

CLYBL

SPIN4

POLR2G

MSH3

THFAP3

SSBP1

GALK1

CMPK2

DOT3

LOC285900

C6ORF160

LHFPL2

15

ACTR1A

CCR1

FDT1

TYW1B

BID

COX5C

POCDA

FAM105A

LOC100128

Y4A4A

MASTL

TM6SF1

HNR1P0

C11ORF17

TTCC3C

MCART1

THCRV4

ZFAND2A

RAB23

CICL10

MEF2A

GTF2H5

LOC653688

DTX2

16

AT2

FLJ10081

KIAA0494

ACSL3

LAPTM5

AKAP13

RAB34

SNAPC2

LOC728993

NHLRC3

DDI60L

TOR3A

MFSD1

LOC728969

MRPL21

POFUT1

SERPINE2

LOC1001284

ARHGAP9

IFT1

ZC3H12C

SRP4P1

LOC728973

LOC7308

17

PRHL2

TYH2

DKC1

HNRPL2

LOC644774

LOC729608

VINT5B

RPK3

LOC100125

CTDG

STAP1

TMEM69

HSD17B11

CHCHD10

POPS

ZNF486

TM6SF19

DNAJC15

TUSC4

IF35

ACTR10

LY96

LOC645157

PTPRE

18

MB9

MAPT01

EXOSC6

ATM

CCDC37

USP34

FAM143A

CEBPA

BCYRN1

TEC

OAS1

HLA-DRA1

SEHL

UIT

CANLG

LOC100130

LOC642956

C10ORF32

TTL

IF44

PLEK

ACIN8

LOC387934

SLC7A8

Figure 14: Tabular Representation of FCM Gene-Sets and Their Enrichment with KEGG Pathways

4.2 Enrichment of User Provided Genes

If there is a user provided gene set, the results for the enrichment of user genes with FCM gene-sets will be displayed as shown in the Figure 15 below.

	C35	C36	C37	C38	C39	C40	C41	C42	C43	C44	C45	C46	C47	C48	C49
KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION	0.15986	0.20181	0.094257	0.70654	0.61489	0.6358	0.085645	0.16337	0.67694	0.79738	0.47505	0.029991	0.25362	0.69698	0.072629
KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	0.22917	0.02059	0.00040081	0.78873	0.70179	0.72217	0.46568	0.0017766	0.76134	0.59434	1.3193e-05	0.0029213	0.12451	0.060583	0.60252
KEGG_NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY	0.11124	0.1424	0.055336	0.6247	0.53363	0.55398	0.32641	9.7232e-05	0.59473	0.12795	0.091665	0.06126	0.54537	0.0022174	0.13215
KEGG_IL1_LIKE_RECEPTOR_SIGNALING_PATHWAY	0.38234	0.0009137	0.0006741	0.55792	0.47023	0.48956	0.28043	0.064969	0.52871	0.65453	3.0293e-06	0.0063884	0.13621	0.042237	0.28663
KEGG_CYTOSOLIC_DNA_SENSING_PATHWAY	0.37231	0.015825	0.031968	0.5457	0.12218	0.13394	0.27247	0.00021753	0.15996	0.26576	4.5863e-05	0.0056454	0.46985	0.038732	0.27241
KEGG_JAK_STAT_SIGNALING_PATHWAY	0.6547	0.0071083	0.2137	0.83495	0.75392	0.7733	0.51631	4.6867e-06	0.48845	0.19548	0.066355	0.23175	0.4192	0.5176	0.027948
KEGG_HEMATOPOIETIC_CELL_LINEAGE	0.096069	0.0029883	0.007779	0.59267	0.15076	0.52285	0.30379	0.081685	0.56296	0.68946	0.37631	0.0089888	0.51441	0.21232	0.32509
KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY	0.040184	0.011503	0.10918	0.36968	0.26542	0.65961	0.40996	0.44292	0.33327	0.50087	0.03004	0.70805	0.2778	0.35761	0.82257
KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY	0.042327	0.22908	0.11434	0.14275	0.27322	0.6672	0.41633	0.1946	0.34235	0.24131	0.1525	0.0074425	0.45841	0.72762	0.51993
KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY	0.0268	0.53587	0.25103	0.30072	0.21103	0.60146	0.3625	0.72737	0.26897	0.41932	0.019839	0.018018	0.59267	0.66292	0.1744
KEGG_FC_EPSILON_RL_SIGNALING_PATHWAY	0.36213	0.093781	0.029165	0.53314	0.44725	0.46609	0.26443	0.58792	0.50441	0.25373	0.32951	0.51175	0.45809	0.52374	0.63465
KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS	0.58067	0.01719	0.37707	0.17513	0.68208	0.33627	0.44768	0.50455	0.38712	0.28868	0.17762	0.15466	0.69403	0.76162	0.29639
KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_IL12_PRODUCTION	0.29748	0.0073219	0.097951	0.45019	0.37222	0.38909	0.21429	0.0042628	0.42379	0.54708	0.0034739	0.10513	0.38191	0.11122	0.54648
INTERFERON_STIMULATED_GENES_SCHOGGINS	0.87416	5.3629e-29	0.088163	0.94137	0.68872	0.87527	0.70263	5.1182e-05	0.91745	0.99967	1.7225e-60	0.023966	0.56646	0.35888	0.95783
Enrichment (P-Value) of Figs gene-sets in user-defined genes	5.0207079	0.614315	0.523609	0.543834	0.318949	0.0223177	0.584044	0.710774	3.9648e-16	0.00167989	0.53527	0.0620247	0.351105		
Total genes found in fuzzy clusters	1	0	0	0	0	0	3	0	0	12	4	0	2	1	

P-values from hypergeometric test to represent significant overlap between FCM gene-sets and the user provided gene-sets. The p-values that are less than the user defined p-value threshold are highlighted with red color.

Figure 15: Enrichment of User Genes with FCM Gene-Sets

4.3 Overlap among KEGG Pathways

There are overlap found among the KEGG pathways as displayed as interactive circular graph (Figure 16). Each node of the circular graph represents KEGG pathway as labelled where a line or an arc between the two nodes shows the existence of common genes between the two pathways. The width of the line/arc corresponds to the number of common genes between the two pathways.

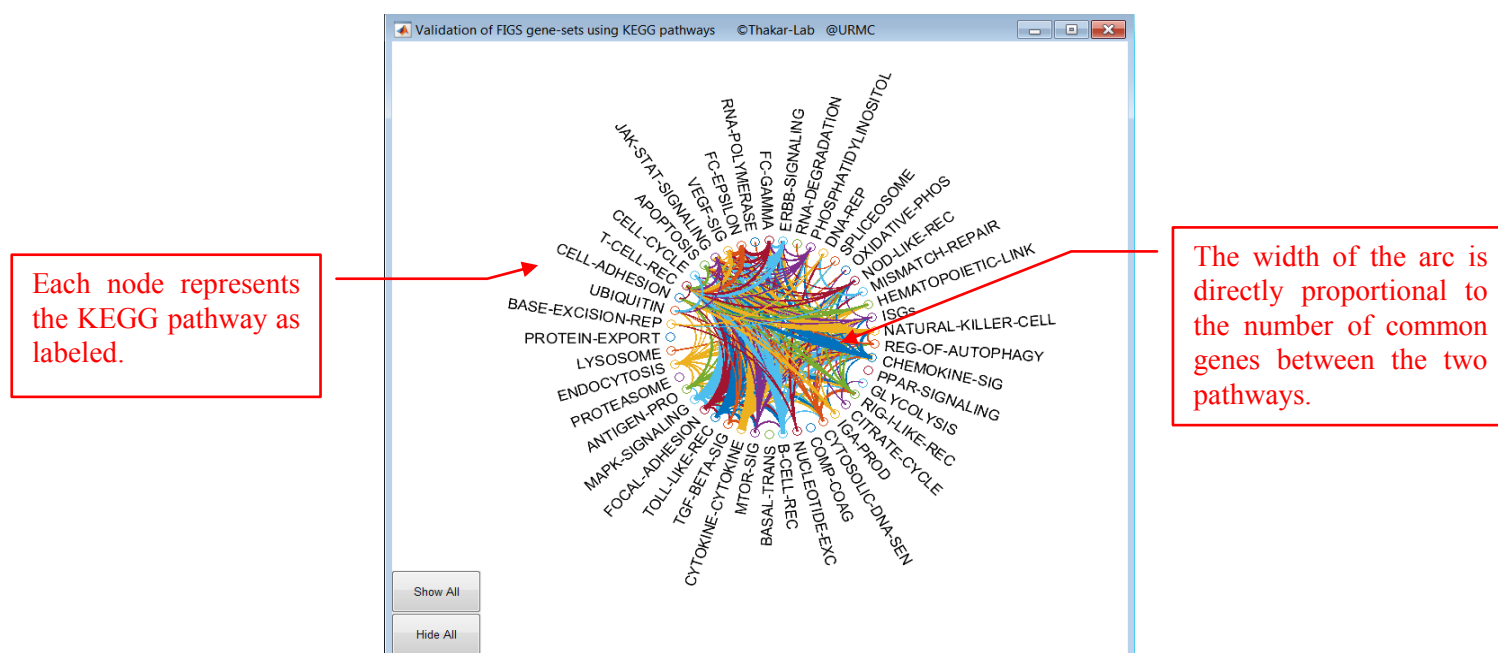


Figure 16: Overlap among KEGG Pathways

4.4 Overlap between Fuzzy Gene-Sets

The overlap among FCM gene-sets are displayed a separate interactive circular graph (Figure 17). In addition to the representation of an overlap, each cluster is labelled with the KEGG that was most significantly enriched by that cluster.

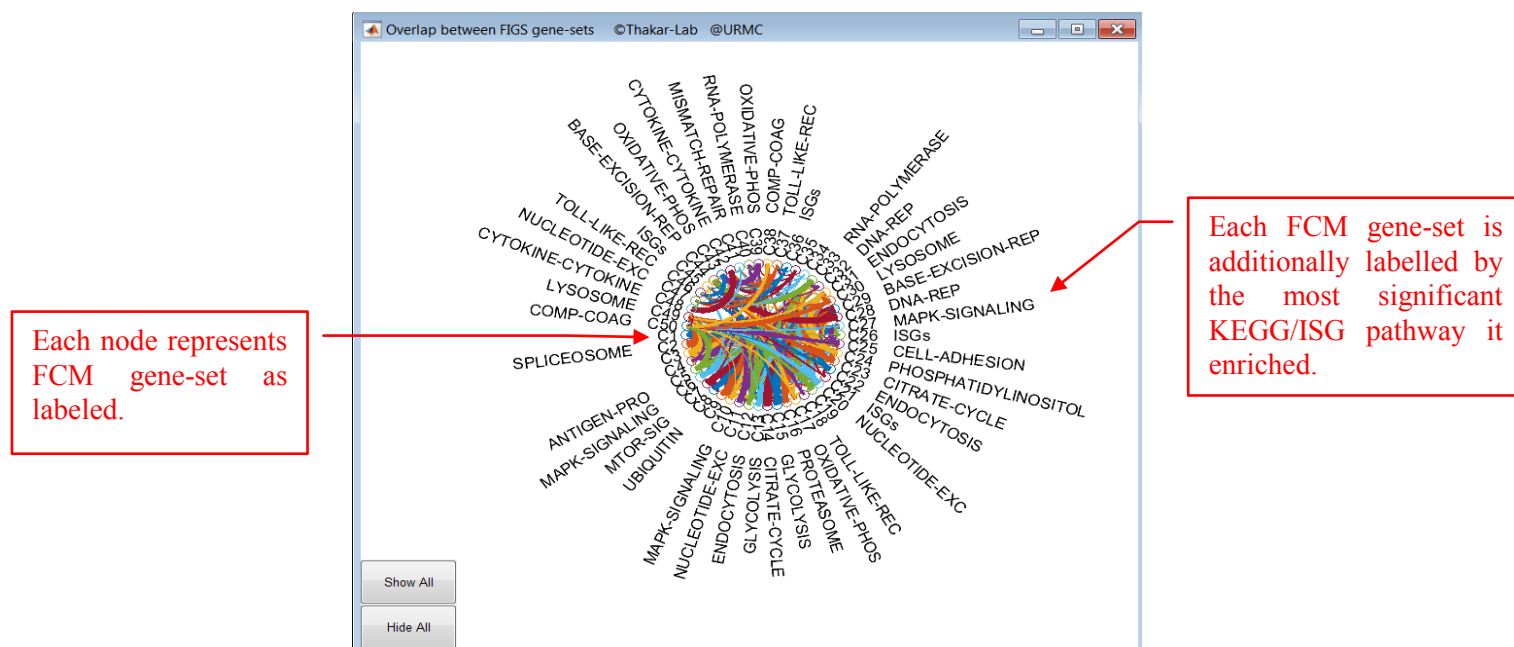


Figure 17: Overlap among FCM Gene-Sets

4.5 Interactive Circular Graphs

The overlap among KEGG pathways and among FCM gene-sets are represented by interactive circular graphs (Figure 18). User can select/hide the nodes by mouse clicks. A single mouse click on a node will change its state from 'show connection' to 'hide connections' and vice versa.



Figure 18: Overlap among FCM Gene-Sets

4.6 Temporal Expression Profile of Gene-Sets

From the drop down menu, the temporal expression of any two clusters can be compared at a time.

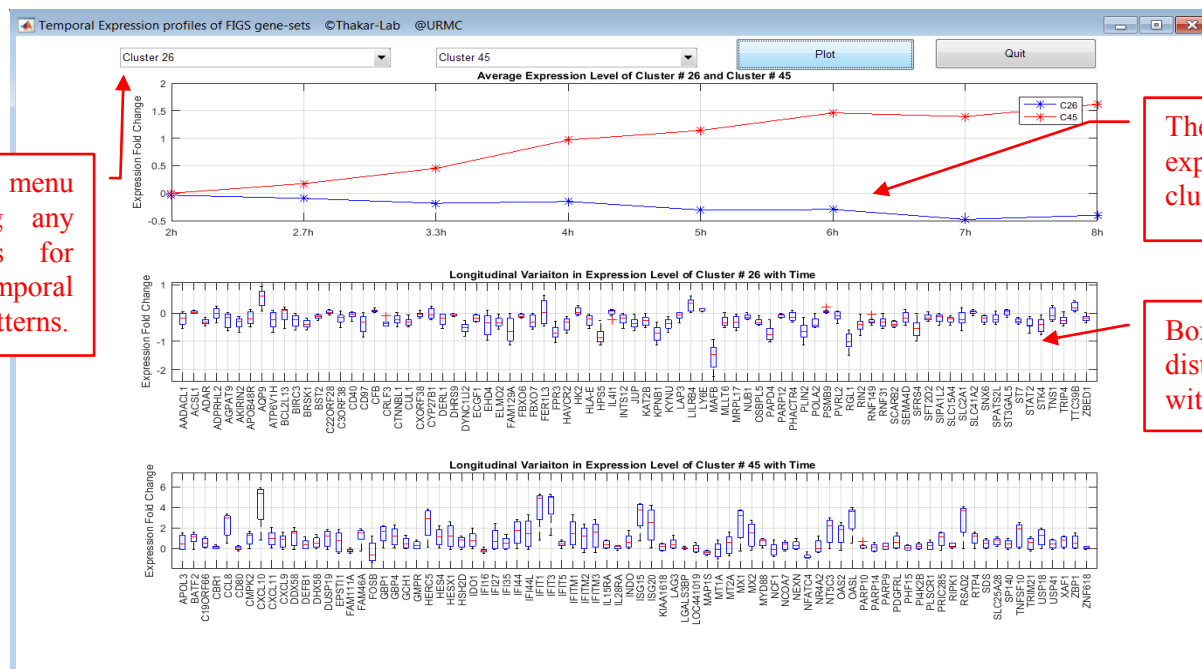


Figure 19: Temporal Expression Pattern of FCM Gene-Sets

4.7 Saving the Results

The detailed results are displayed in the tabular form (see section 4.1). A copy of the data-driven FCM gene-sets will be generated and saved as “FIGS_Results.csv”. This results file can be found in the installation folder of FIGS.

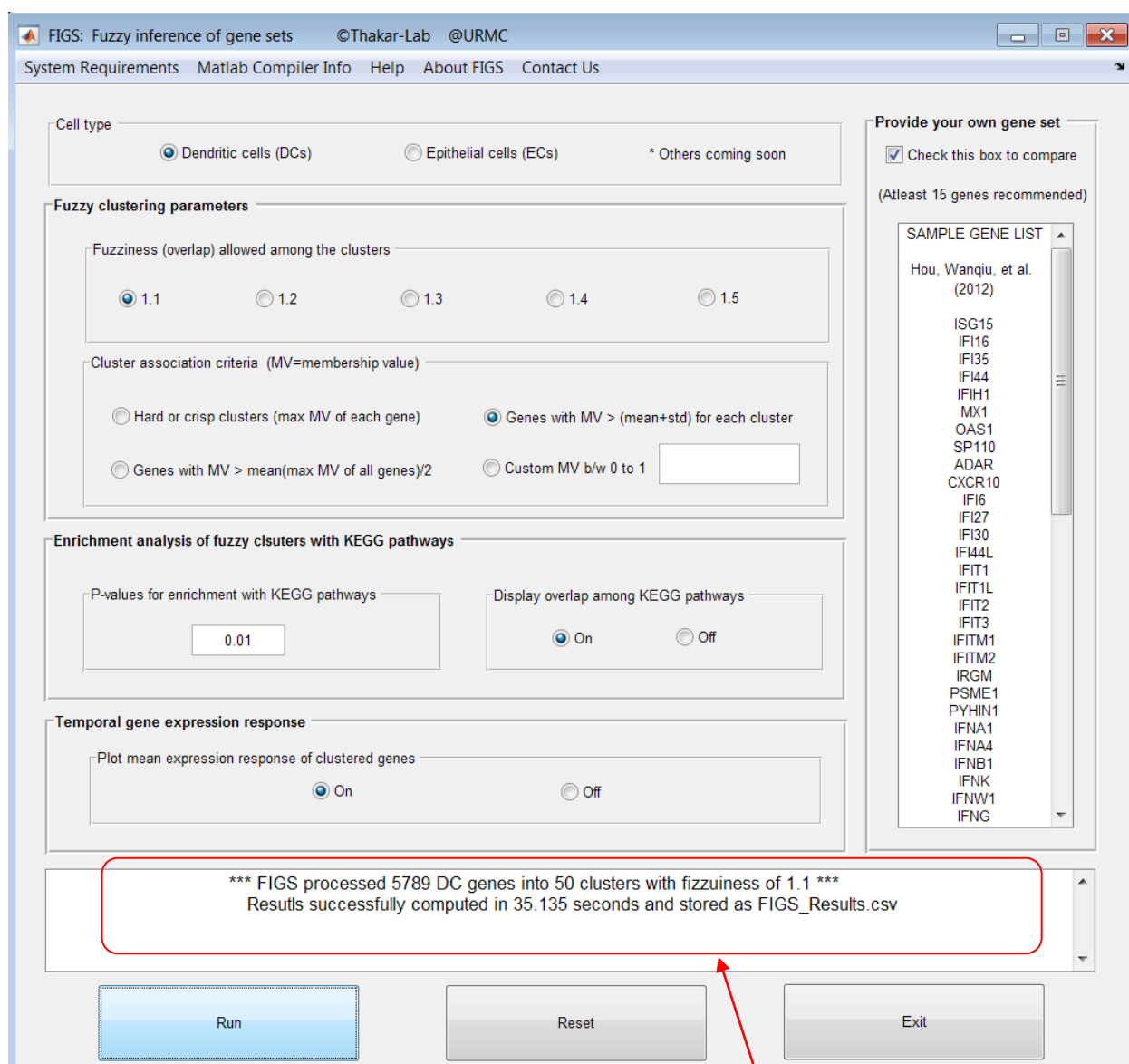


Figure 20: FIGS Results

The gene-sets produced by FIGS will be stored as FIGS_Results.csv file.