Canadian Bioinformatics Workshops

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bioinformaticsdotca.github.io
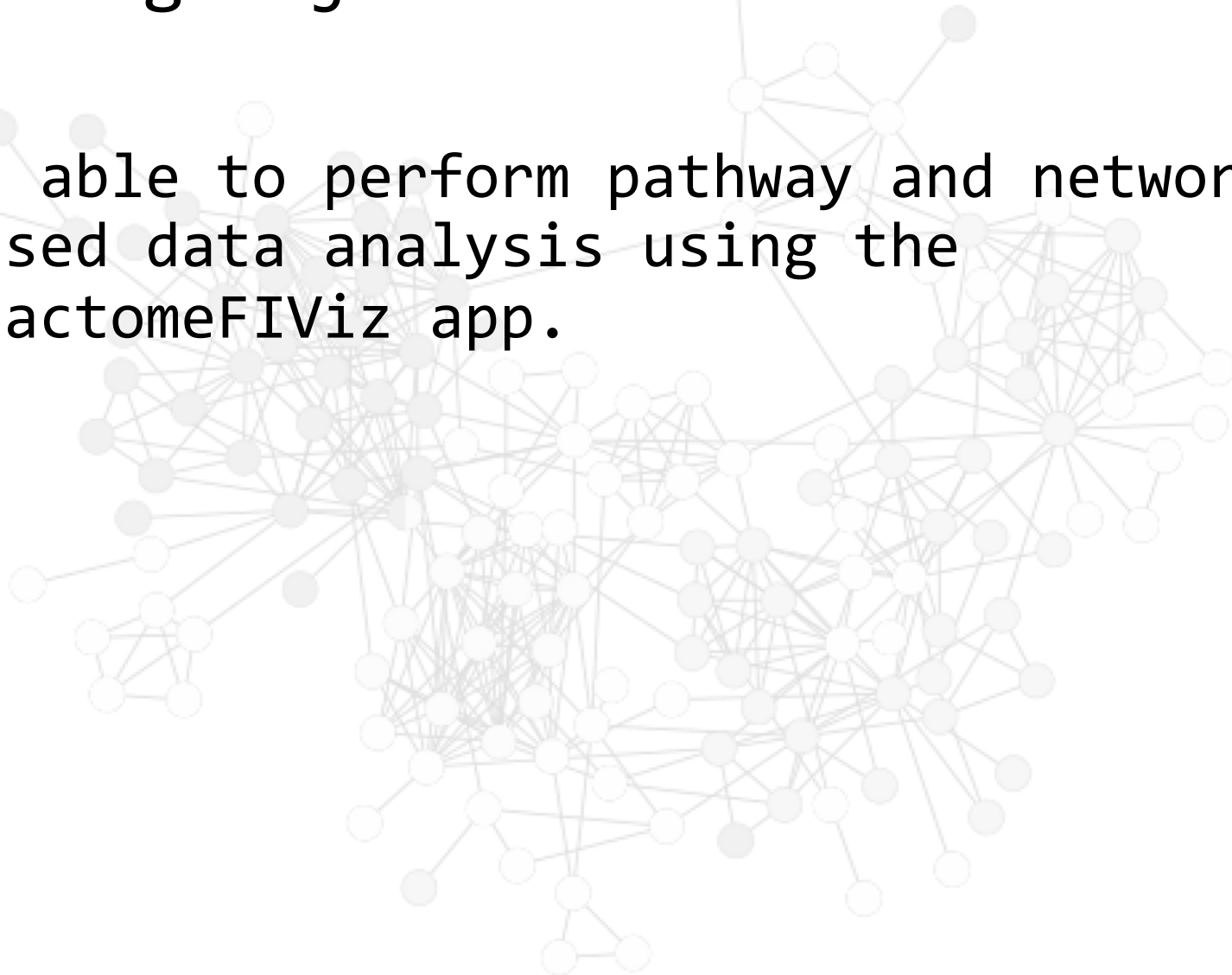
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Learning Objectives of Module

- Be able to perform pathway and network-based data analysis using the ReactomeFIViz app.

Major Features in ReactomeFIViz

- Pathway and Network Analysis Features:
  - Support pathway enrichment analysis: Binomial test and GSEA.
  - Integration of Reactome Voronoi map for pathway holistic view.
  - Perform Boolean network and PGM-based pathway modeling
  - Construct FI subnetwork.
  - Support for HotNet analysis.
  - Perform network clustering.
  - Overlay cancer gene index, gene and cancer drug annotations.
  - Support to mouse pathways and FI network.
  - scRNA-seq data analysis and visualization.
  - Perform survival analysis.

A1) Reactome Pathway Enrichment Analysis

Displaying Reactome Pathways in the FI Network View

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Pathway Enrichment Analysis

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Gene Set Enrichment Analysis (GSEA)

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Visualize Cancer Targetome in Reactome Pathways

A2) De Novo Subnetwork Construction & Clustering
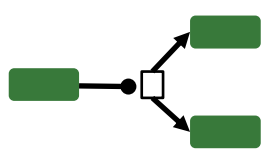
Curated Pathway DBs + Uncurated Interaction Evidence

Machine Learning
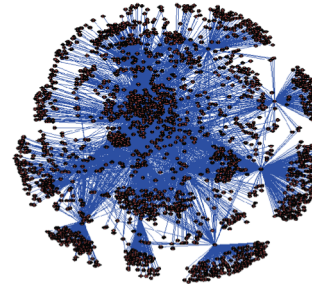
Reactome Functional Interaction Network
(~13K proteins; ~436K interactions)

+

DATA

Project your data into Reactome FI Network
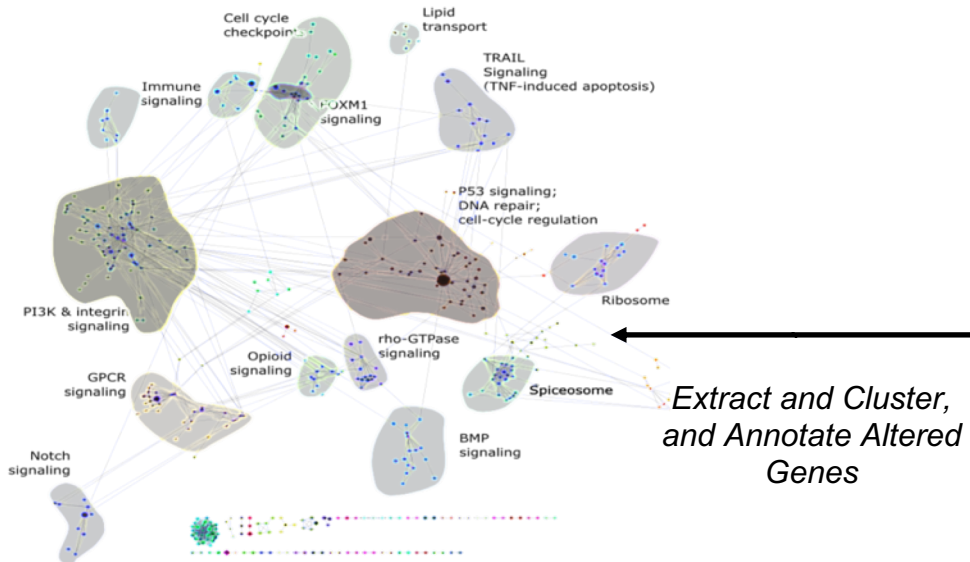
Extract and Cluster, and Annotate Altered Genes

Cell cycle checkpoint

Lipid transport

Immune signaling

TRAIL Signaling (TNF-induced apoptosis)

FOXM1 signaling

P53 signaling; DNA repair; cell-cycle regulation

Ribosome

PI3K & integrin signaling

rho-GTPase signaling

Opioid signaling

Spiceosome

GPCR signaling

BMP signaling

Notch signaling

Disease "modules" (10-30)
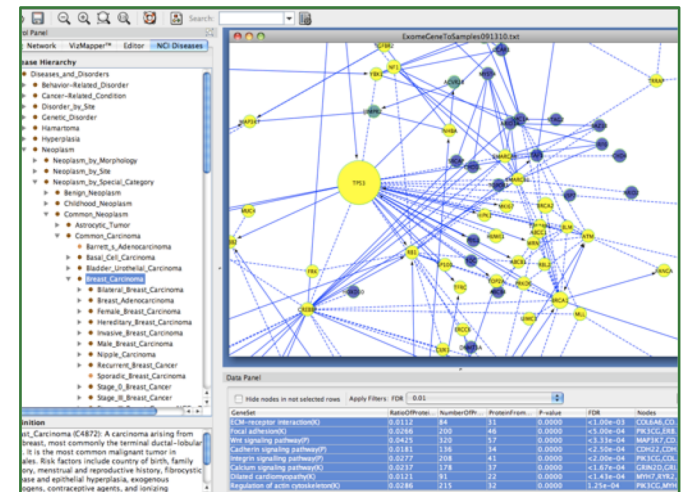
Cytoscape using ReactomeFIViz app

Upload your data
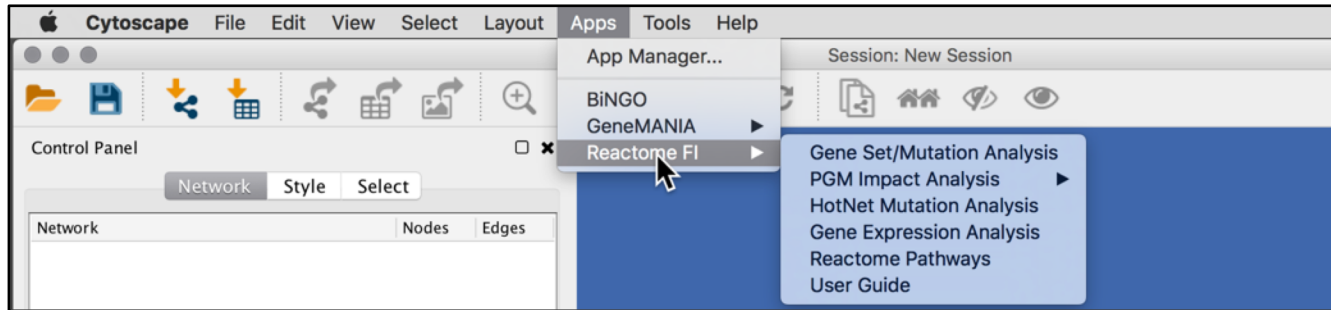
- FI plug-in supports four file formats:
  - Simple gene set: one line per gene
  - Gene/sample number pair. Contains two required columns, gene and number of samples having gene mutated, and an optional third column listing sample names (delimited by semi-colon ;)
  - NCI MAF (mutation annotation file)
  - Sample Gene Expression data file

File Formats

- Choose Plugins, Reactome FIs.

Simple Gene List

MSI2
PTPRT
PELO
SLC18A1
TACC2
FAM148B
PRC1
MSTN
ATP6V1G2
APOE
IMPA2
AGER
XPO5
MEST
RREB1
BAT1
WIPI1

NCI MAF (mutation annotation file)

Hugo_Symbol	Entrez_Gene_	Center	NCBI_Build	Chromosome	Start_position	End_position	Strand
BAI2	576	broad.mit.edu	36	1	31974808	31974808	+
LRRC41	10489	broad.mit.edu	36	1	46524584	46524584	+
C1orf173	127254	broad.mit.edu	36	1	74828082	74828082	+
SSX2IP	117178	broad.mit.edu	36	1	84900740	84900740	+
NTNG1	22854	broad.mit.edu	36	1	107668441	107668441	+
PGLYRP3	114771	broad.mit.edu	36	1	151541551	151541551	+
FCRL5	83416	broad.mit.edu	36	1	155783467	155783467	+
FBXO28	23219	broad.mit.edu	36	1	222388418	222388418	+
OR2M2	391194	broad.mit.edu	36	1	246410342	246410342	+
MKX	283078	broad.mit.edu	36	10	28063690	28063690	+
......							

Variant_Classification	Variant_Type	Reference_Allele	Tumor_Seq_Allele1	Tumor_Seq_	dbSNP_RS	dbSNP_Val_	Tumor_Samp
Missense_Mutation	SNP	C	C	G	novel	none	TCGA-04-1331
Missense_Mutation	SNP	C	C	T	novel	none	TCGA-04-1331
Missense_Mutation	SNP	T	T	G	novel	none	TCGA-04-1331
Silent	SNP	A	A	G	novel	none	TCGA-04-1331
Missense_Mutation	SNP	G	G	A	novel	none	TCGA-04-1331
Missense_Mutation	SNP	G	G	T	novel	none	TCGA-04-1331
Missense_Mutation	SNP	A	A	C	novel	none	TCGA-04-1331
Missense_Mutation	SNP	A	A	T	novel	none	TCGA-04-1331
Missense_Mutation	SNP	G	G	A	novel	none	TCGA-04-1331
Missense_Mutation	SNP	C	C	A	novel	none	TCGA-04-1331

Matched_No	Match_Norm	Match_Norm	Tumor_Valid	Tumor_Valid	Match_Norm	Match_Norm	Verification_	Validation_S	Mutation_St	Sequencing_	Sequence_S	Validation_M	Score	BAM_file	Sequencer
TCGA-04-1331-10A-01W							Unknown	Unknown	Unknown	x	x	---		x
TCGA-04-1331-10A-01W							Unknown	Unknown	Unknown	x	x	---		x
TCGA-04-1331-10A-01W							Unknown	Unknown	Unknown	x	x	---		x
TCGA-04-1331-10A-01W							Unknown	Unknown	Unknown	x	x	---		x
TCGA-04-1331-10A-01W							Unknown	Unknown	Unknown	x	x	---		x
TCGA-04-1331-10A-01W							Unknown	Unknown	Unknown	x	x	---		x
TCGA-04-1331-10A-01W							Unknown	Unknown	Unknown	x	x	---		x
TCGA-04-1331-10A-01W							Unknown	Unknown	Unknown	x	x	---		x
TCGA-04-1331-10A-01W							Unknown	Unknown	Unknown	x	x	---		x
TCGA-04-1331-10A-01W							Unknown	Unknown	Unknown	x	x	---		x

Gene/Sample Number Pairs

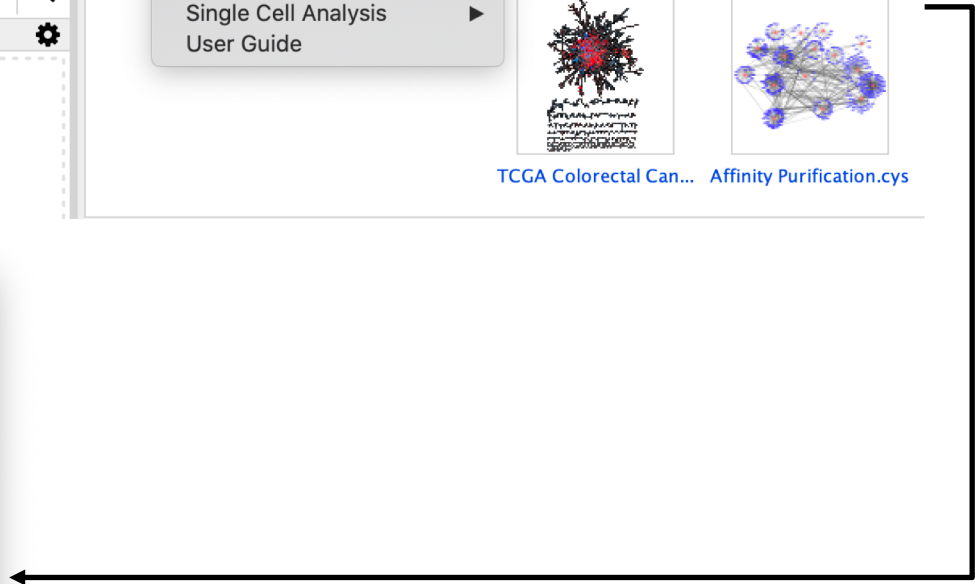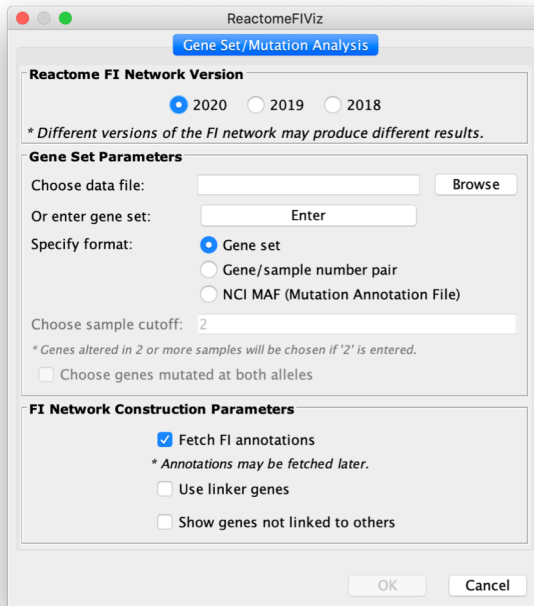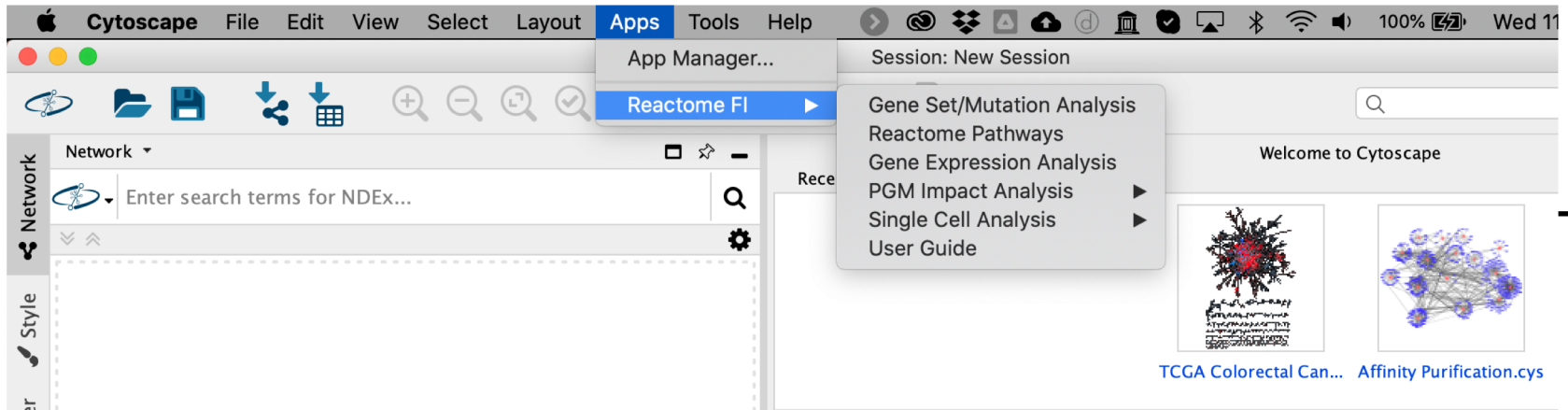| Gene	Sample_Number	Samples
IFT88	1	TCGA-10-0937
TACC2	5	TCGA-24-2288;TCGA-09-1662;TCGA-13-0755;TCGA-13-0920;TCGA-24-2035
ADAD2	1	TCGA-24-1419
PODXL2	1	TCGA-24-2290
RTN3	1	TCGA-13-0726
TADA2B	1	TCGA-25-1313
CD274	1	TCGA-25-1627
SULF1	2	TCGA-24-2262;TCGA-09-2056
SYCP2	3	TCGA-24-1563;TCGA-61-2008;TCGA-24-1427
CD200R1L	1	TCGA-13-1488
RCBTB2	1	TCGA-61-2113
TOP2B	1	TCGA-13-0923
C1orf50	1	TCGA-25-2392
ATP9A	5	TCGA-25-1329;TCGA-04-1530;TCGA-24-2262;TCGA-10-0933;TCGA-13-0795
NUDT5	1	TCGA-61-2003
ZNF189	1	TCGA-24-2254
KCNB1	1	TCGA-23-1028
FERMT3	1	TCGA-24-1464
ZCCHC2	1	TCGA-61-1998
DDX18	1	TCGA-13-1509
TGM1	2	TCGA-24-0975;TCGA-25-1321
SAMD7	1	TCGA-09-2051
OR2F2	3	TCGA-13-0723;TCGA-24-2267;TCGA-25-2392
ZSWIM3	2	TCGA-24-1466;TCGA-23-1118
EIF2AK2	2	TCGA-59-2355;TCGA-24-1463
KIAA2018	4	TCGA-23-1024;TCGA-04-1367;TCGA-24-2288;TCGA-24-2289
......		

Microarray (array) data file

gene	Sample 122	Sample 123	Sample 124	Sample 125	Sample 126	Sample 127	Sample 128	Sample 129	Sample 130
IFT88	1.433357937	0.749571365	0.204170171	1.376375723	0.049504161	0.912377692	0.464660294	0.106486375	0.40767808
KIF9	0.349692236	-0.093947168	-0.568902295	0.177455762	-0.30793794	-0.574121582	-0.772454492	0.850743799	0.19833291
CPSF3	-0.628846878	-0.519774777	0.200101088	-0.388888256	-0.094393584	0.549131811	0.44005971	-0.247094525	1.421708617
TACC2	0.985299156	-0.732555355	1.013646591	-0.057886422	0.730172249	0.554418157	1.280112472	0.463706367	0.956951722
C14orf132	1.249528811	0.104876045	0.524096007	-0.43464182	-1.528259113	-0.467450338	-0.715336925	-0.525776594	-1.06893985
RTN3	0.10643433	-0.286920286	-0.329065423	0.548958273	1.054699921	-0.827782882	-0.462525025	1.39888521	-0.588960437
PODXL2	-0.031430138	-0.390413822	-0.075387324	-0.412392415	0.085789024	-0.097365917	-0.053408731	-0.104692114	1.43380939
CORO1A	-0.247037235	0.664838693	-0.423713196	-0.001970579	0.488162732	-0.435111645	0.596447999	-0.463607768	0.055021666
RBM17	-0.360070659	-0.142165087	-0.233914802	0.018396914	-0.130696373	-0.394476802	-0.818819233	-0.692663375	0.993237633
WT1	-0.768498156	-0.669419285	-0.763665041	-0.674252401	-0.618671571	-0.393931693	-0.906241952	-0.35285021	-0.538925163
SULF1	-0.863622291	1.588947769	0.272263522	-0.419487008	0.401966747	-0.081472544	-1.17805435	0.327289133	-0.21903657
SYCP2	-0.365259803	1.246319117	-0.107066702	0.891658263	0.914356558	0.091543376	-1.037696782	0.727095627	0.009262058
PHYH	-0.252934465	-0.340129465	0.084219531	-0.613340462	-1.85732245	0.479503528	0.22954453	-1.130697457	1.037551523
RCBTB2	-1.216044791	1.137367735	-0.741461602	0.636779988	-0.695953625	-0.46841374	-0.344892088	-0.130354482	-0.572431973
TOP2B	1.329376011	1.272684609	0.636481097	0.611284918	0.466406891	0.982928554	-0.749308731	0.397117399	0.050669942
SEC22B	-0.712050988	0.661526326	-0.33943161	0.917245507	0.427725933	0.413113408	-0.638988365	0.632301277	0.486176031
ATP9A	1.547427859	0.444111328	1.415509578	-0.14352465	0.540051896	0.510070468	-0.233468933	-0.149520936	-0.047584083
TGFBR1	-0.782212802	-0.264862477	-0.123008356	0.027190126	-0.239829397	0.427719409	-0.773868442	0.110633726	1.270499777
NUDT5	-0.616643202	-0.117594702	0.072831699	-0.025664715	0.37488737	0.433985219	-0.89899959	0.020300278	0.112230265
VTI1B	1.252187159	0.515526231	0.073529674	0.770902019	-0.368466883	-1.684634408	0.191395423	0.967344934	2.116535981
RPS6KB1	-0.387163384	0.639591396	-0.597648114	-0.392297158	0.932216509	1.563670699	-0.782463975	0.465043084	-0.674654723
RAPGEF4	0.202545341	0.240920292	0.106607963	1.564856103	0.557513638	-0.027704365	-0.651297319	-0.612922368	-1.178952896
PRO1596	-0.010404297	0.228155239	0.228155239	0.445509484	0.148635394	0.079718194	-0.376195587	0.138032748	0.03730761
KCNB1	0.093447081	-0.061401218	0.135678435	0.628377569	0.656531805	1.458927537	1.318156356	-0.469637643	0.346835207
ALDH9A1	0.702468807	-0.111692273	0.963729452	-1.181038168	-1.083824904	1.698904754	1.844724649	-0.038782325	-1.545587905
ZCCHC2	0.55864339	0.120590563	0.845270548	-0.479704052	0.477522496	-1.144895382	-0.398583158	0.55323533	-0.095731821
LOC51274	-0.291416641	-0.264217345	0.134705668	-0.527143876	-0.073822271	-0.699406086	-0.971399049	-0.218885185	-0.146353728
DDX18	0.34967191	0.294984327	-1.00840307	1.015037505	0.140036175	0.076233995	-0.160745532	0.51373466	1.069725088

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Gene Set-based Analysis
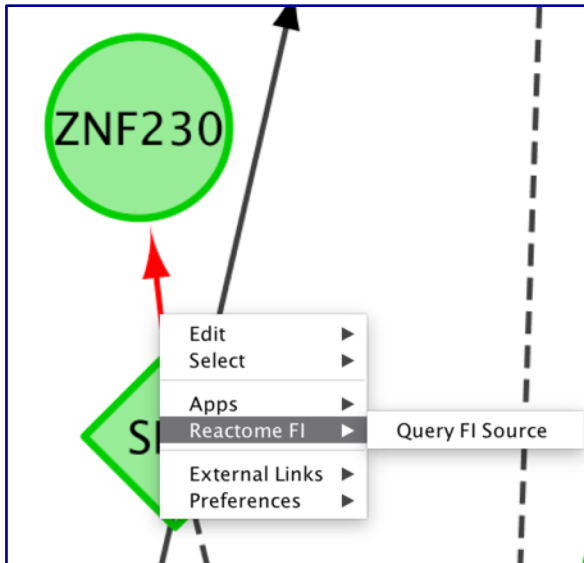
FI Results Display

- Constructed network is displayed in the Network View panel using an FI specific visual style

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FI Annotations

- Provides detailed information on selected FIs.

- Three edge attributes are created:
  - FI Annotation.
  - FI Direction.
  - FI Score (for predicted FI).

- Edges display direction attribute values.
  - --> for activating/catalyzing.
  - --| for inhibition.
  - solid line for complexes or inputs.
  - --- for predicted FIs.
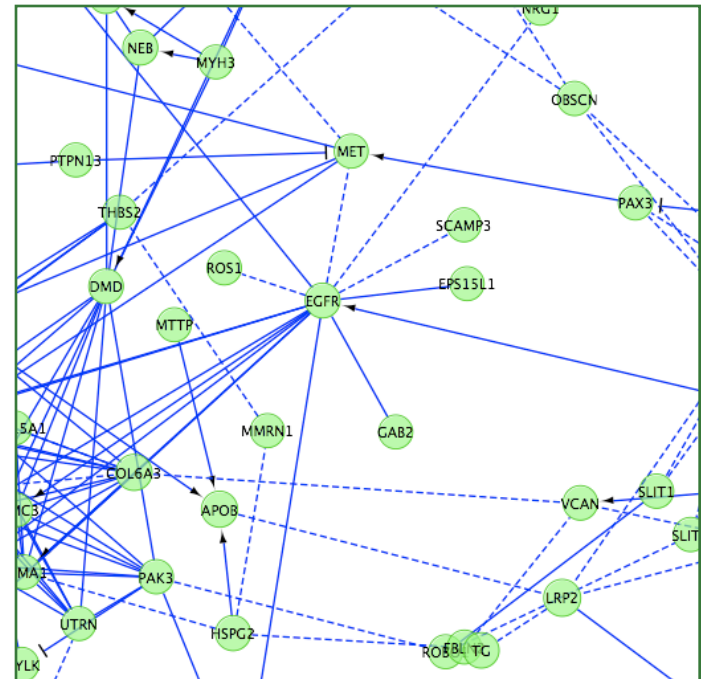
Query FI Source

Annotated FIs

Predicted FIs

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Cluster FI Network

- Runs spectral partition based network clustering ([Newman, 2006](#)) on the displayed FI network.

- Nodes in different network modules will be shown in different colours (max 15 colours).

- Analyze cancer mutation data with HotNet algorithm ([Vandin, 2012](#))
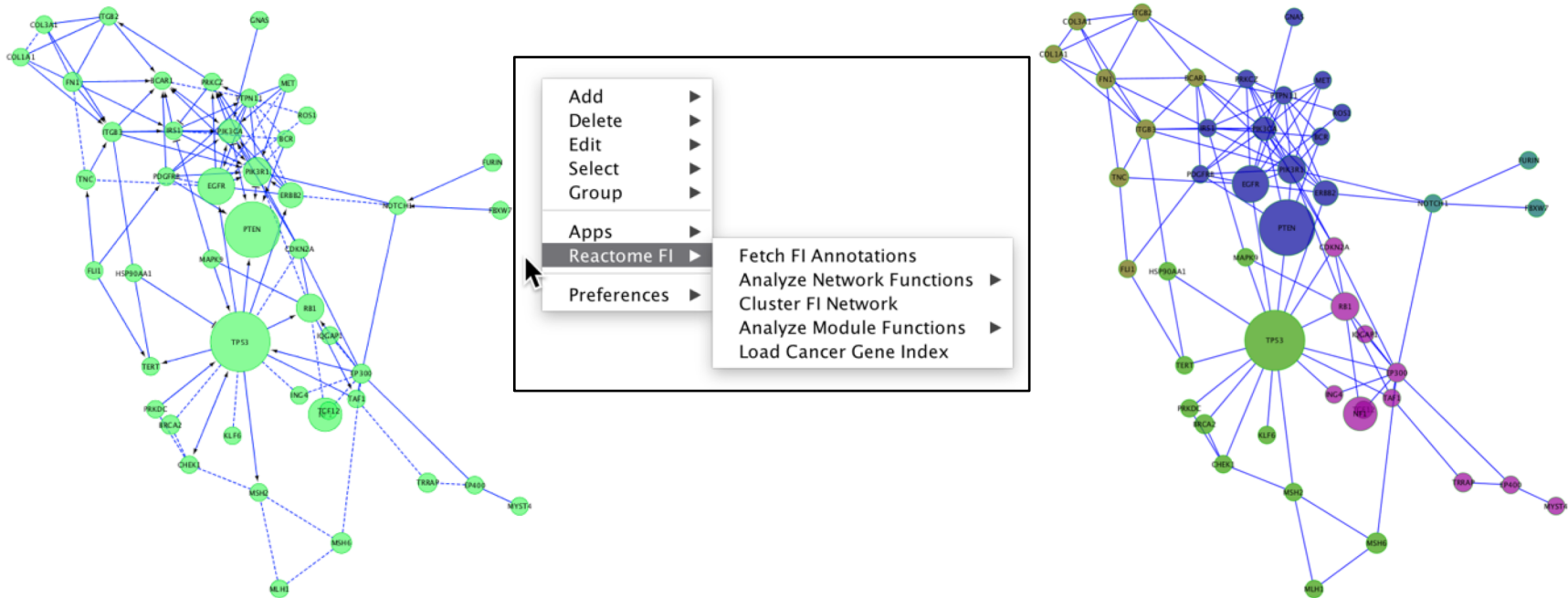
Analyze Module Functions

- Pathway or GO term enrichment analysis on individual network modules.
  - Use filter to remove small network m...
  - Filter by FDR

Show Pathway Diagrams

- Select a pathway in "Pathways in Network/Modules" tabs, right click, select "Show Pathway Diagram"
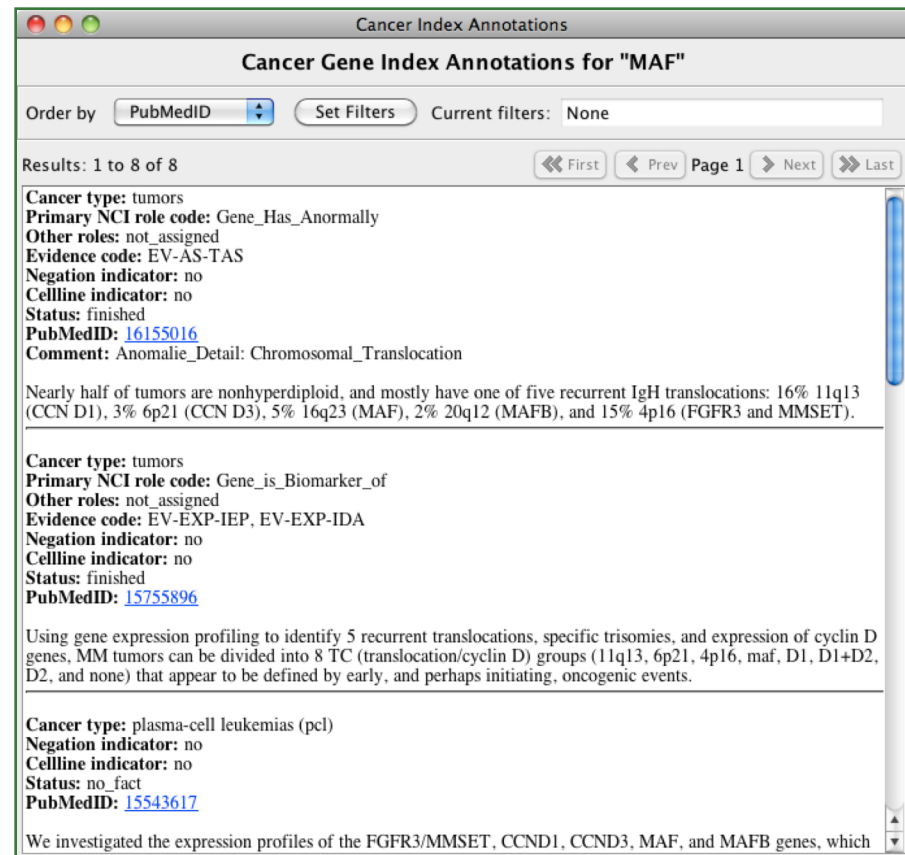
NCI Cancer Gene Index

- View detailed annotations for the selected gene or protein.
- Annotations are sortable by PubMed ID, Cancer type, status, and other criteria.

Overlay Cancer Gene Index

- Load the NCI disease terms hierarchy in the left panel.
- Select a disease term in the tree to select all nodes that have this annotation or one of its sub-terms.
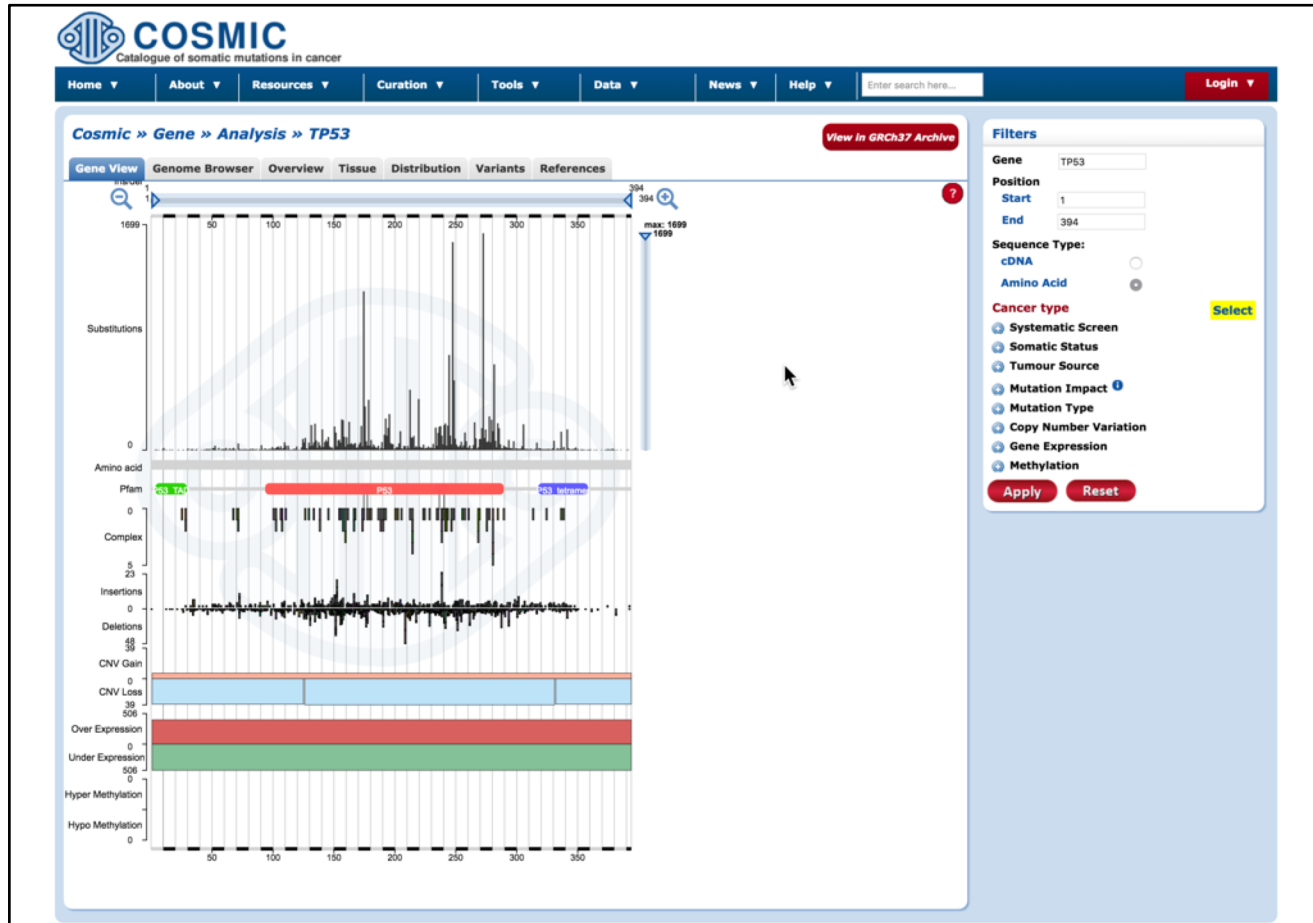
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Visualize Cancer Targetome in the Reactome FI Network
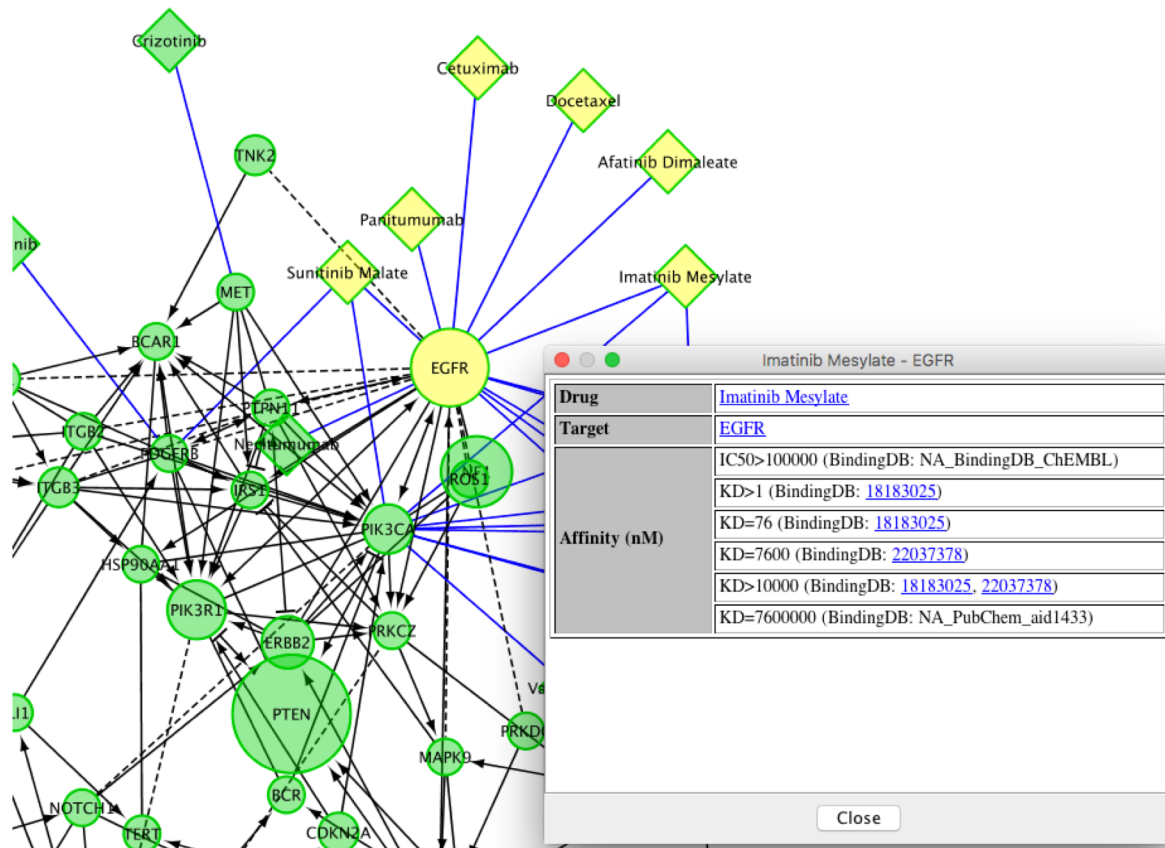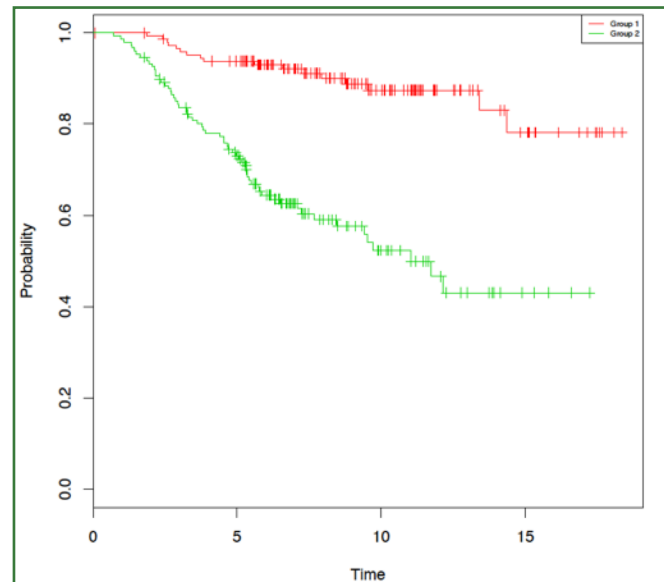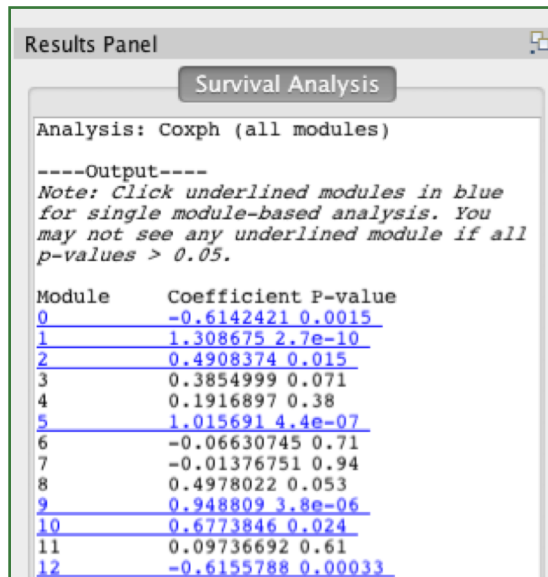

TCGA GBM Mutation Profile

COSMIC

- View detailed variant annotations for the selected gene or protein from COSMIC database.

Module Based Survival Analysis

- Discover Prognostic Signatures in Disease Module Datasets.

- Based on a server-side R script that runs either CoxPH or Kaplan-Meyer survival analysis.

- Requires appropriate clinical data file.

Demos

REACTOMEFIVIZ APP

We are on a Coffee Break & Networking Session

Workshop Sponsors: