Reactome Functional Interaction Network and ReactomeFIViz app

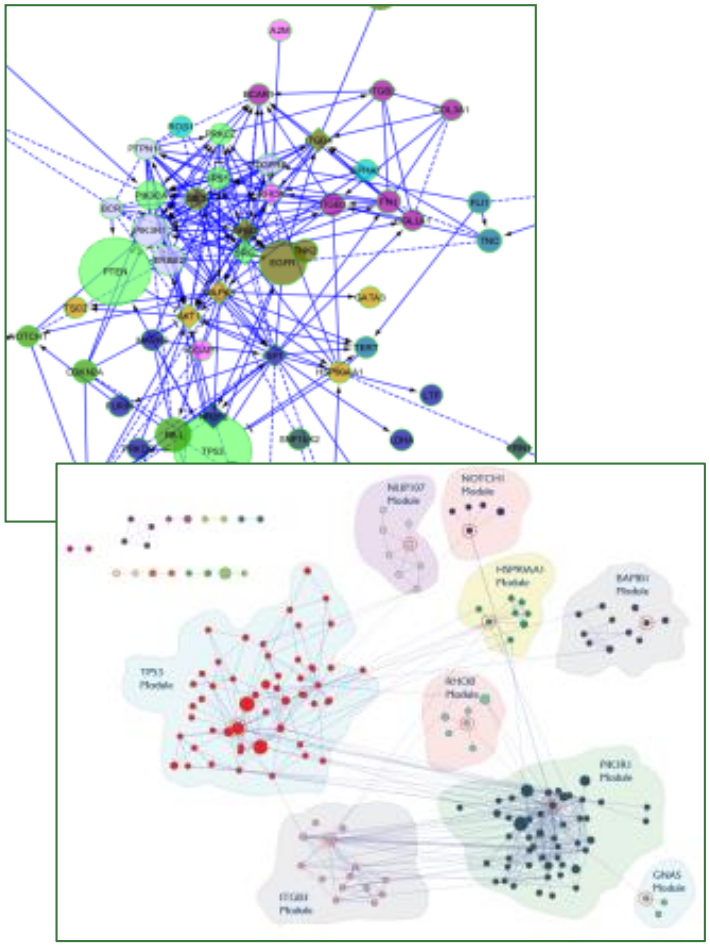
Contact: help@reactome.org

Learning Objectives of Module

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

Reactome Functional Interaction (FI) Network and ReactomeFIViz app

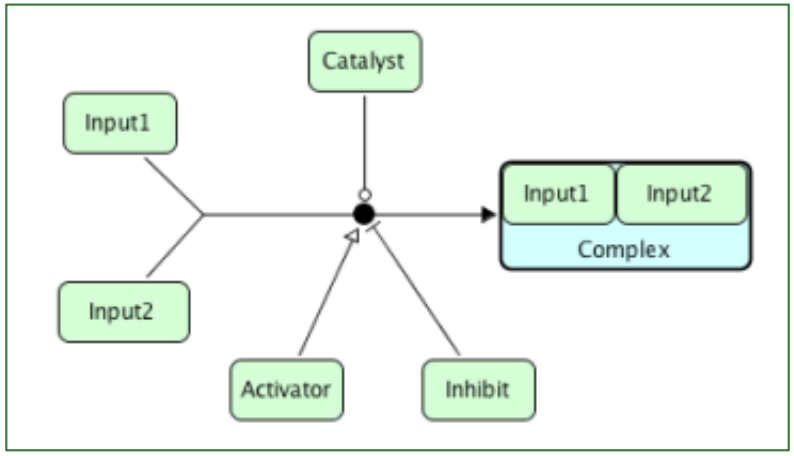
- No single mutated gene is necessary and sufficient to cause cancer.
  - Typically one or two common mutations (e.g. TP53) plus rare mutations.
- Analyzing mutated genes in a network context:
  - reveals relationships among these genes.
  - can elucidate mechanism of action of drivers.
  - facilitates hypothesis generation on roles of these genes in disease phenotype.
- Network analysis reduces hundreds of mutated genes to < dozen mutated pathways.



What is a Functional Interaction?

- Convert reactions in pathways into pair-wise relationships
  - **Functional Interaction**: an interaction in which two proteins are involved in the same reaction as input, catalyst, activator and/or inhibitor, or as components in a complex

Reaction

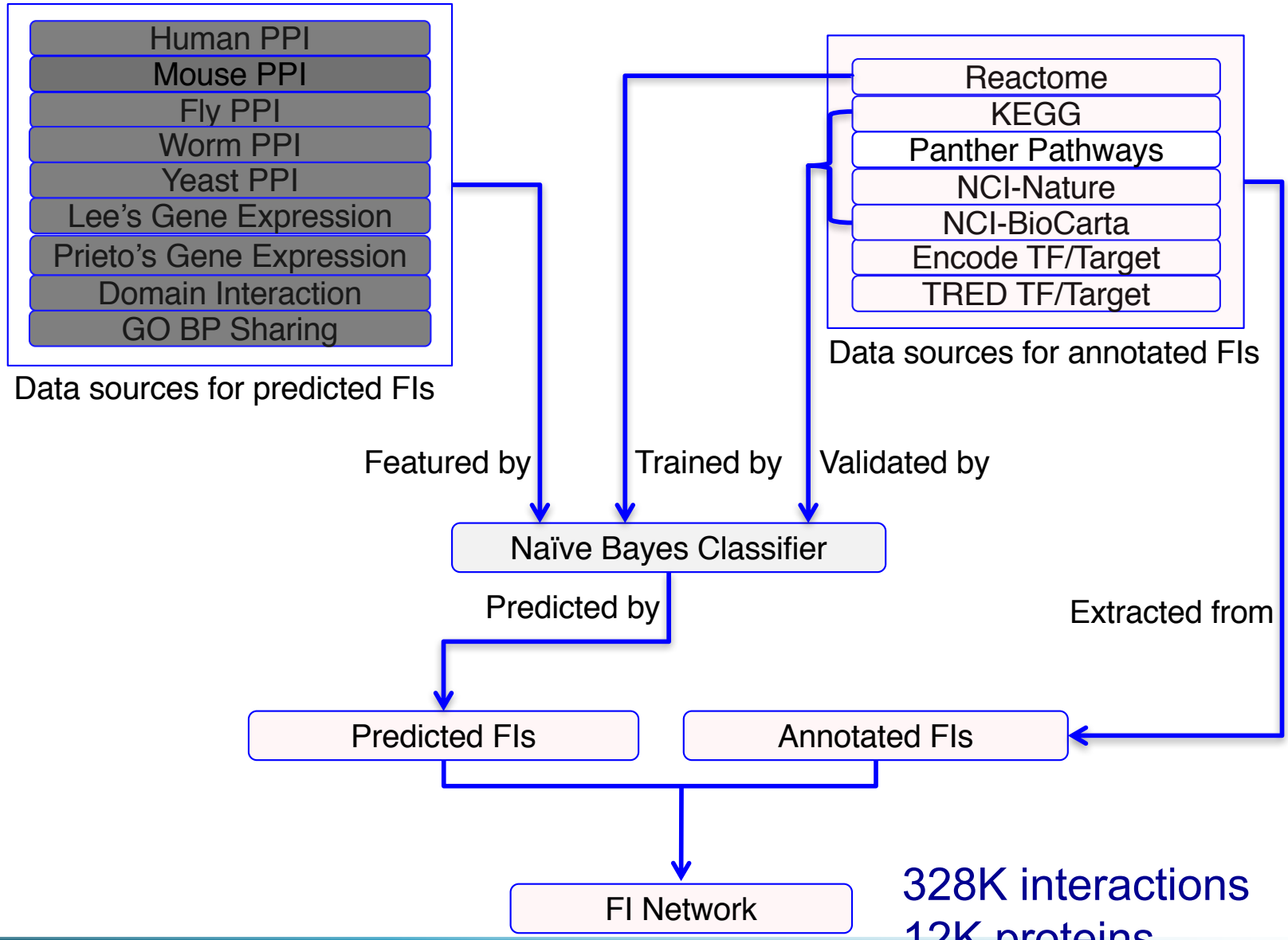


Functional Interactions

Input1-Input2, Input1-Catalyst, Input1-Activator, Input1-Inhibitor, Input2-Catalyst, Input2-Activator, Input2-Inhibtior, Catalyst-Activator, Catalyst-Inhibitor, Activator-Inhibitor

Method and practical application: A human functional protein interaction network and its application to cancer data analysis, Wu et al. 2010 Genome Biology.

Construction of the FI Network

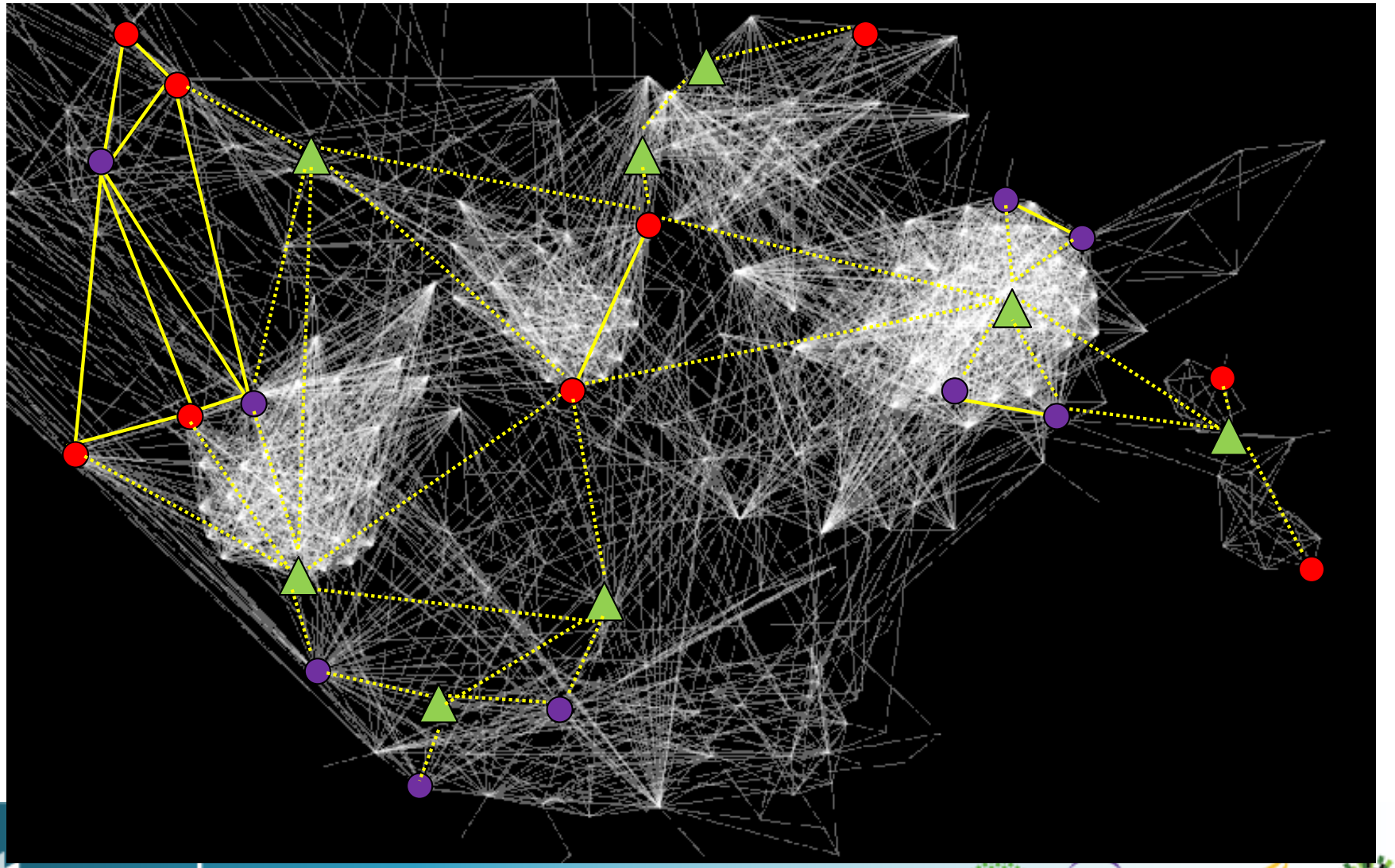


328K interactions
12K proteins

reactome

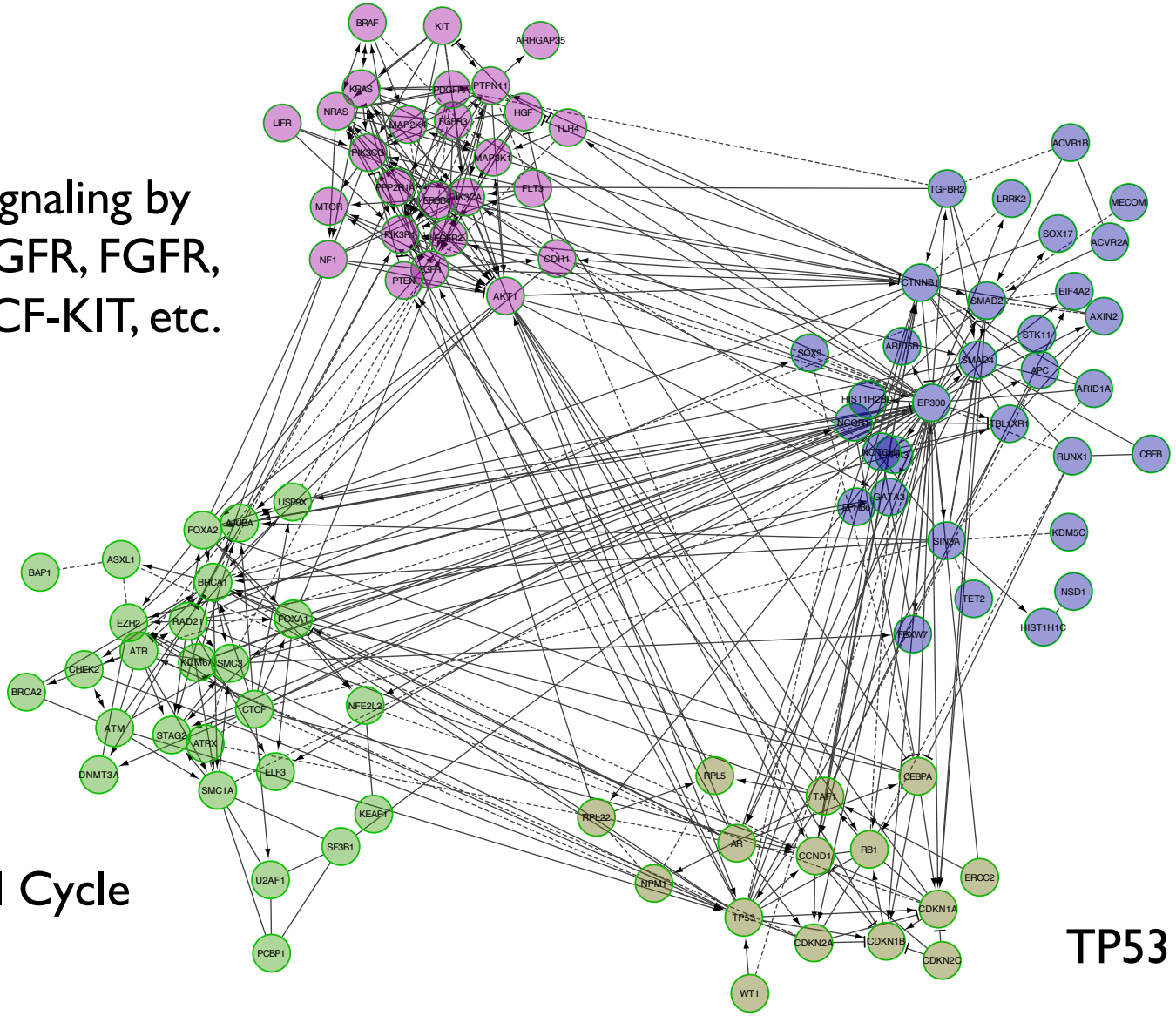
EMBL-EBI NYU Langone MEDICAL CENTER OHSU OICR

Projecting Experimental Data onto FI Network



127 Cancer Driver Genes

Signaling by EGFR, FGFR, SCF-KIT, etc.



Signaling by Notch, Wnt, TGF-beta, SMAD2/3, etc.

Cell Cycle

TP53 Pathway

reactome

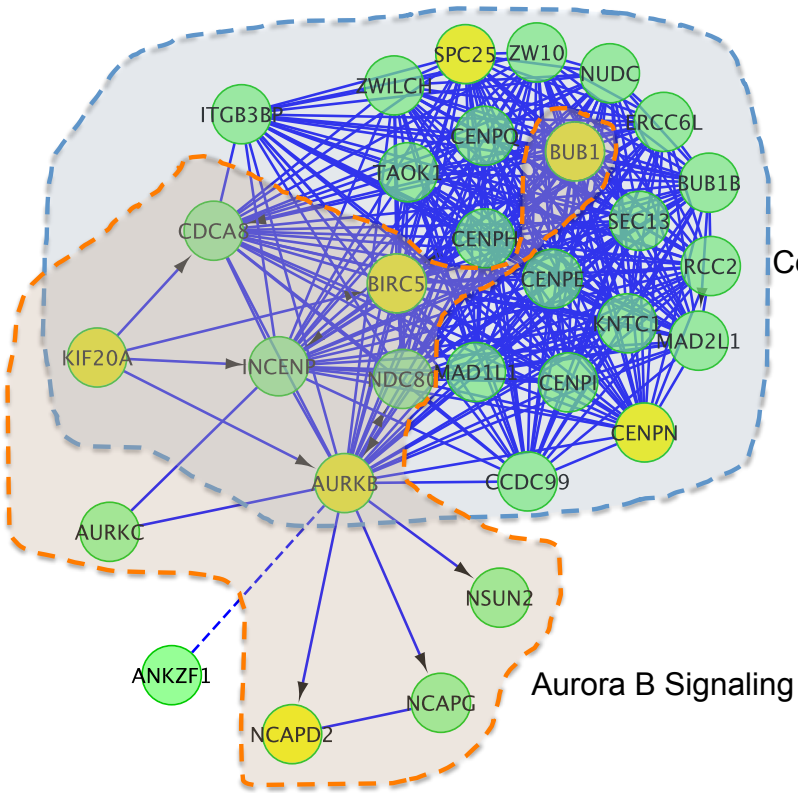
EMBL-EBI

NYU Langone MEDICAL CENTER

OHSU

OICR

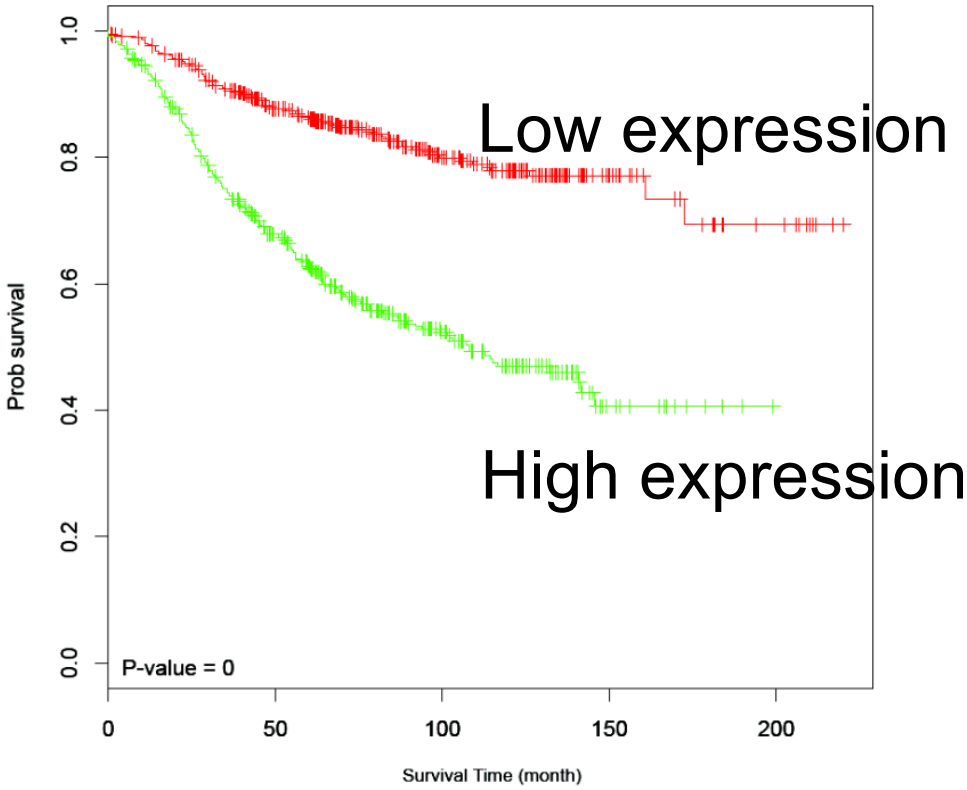
Module-Based Prognostic Biomarker in ER+ Breast Cancer



Cell Cycle M Phase

Aurora B Signaling

Measure levels of expression of the genes in this network module



reactome

EMBL-EBI

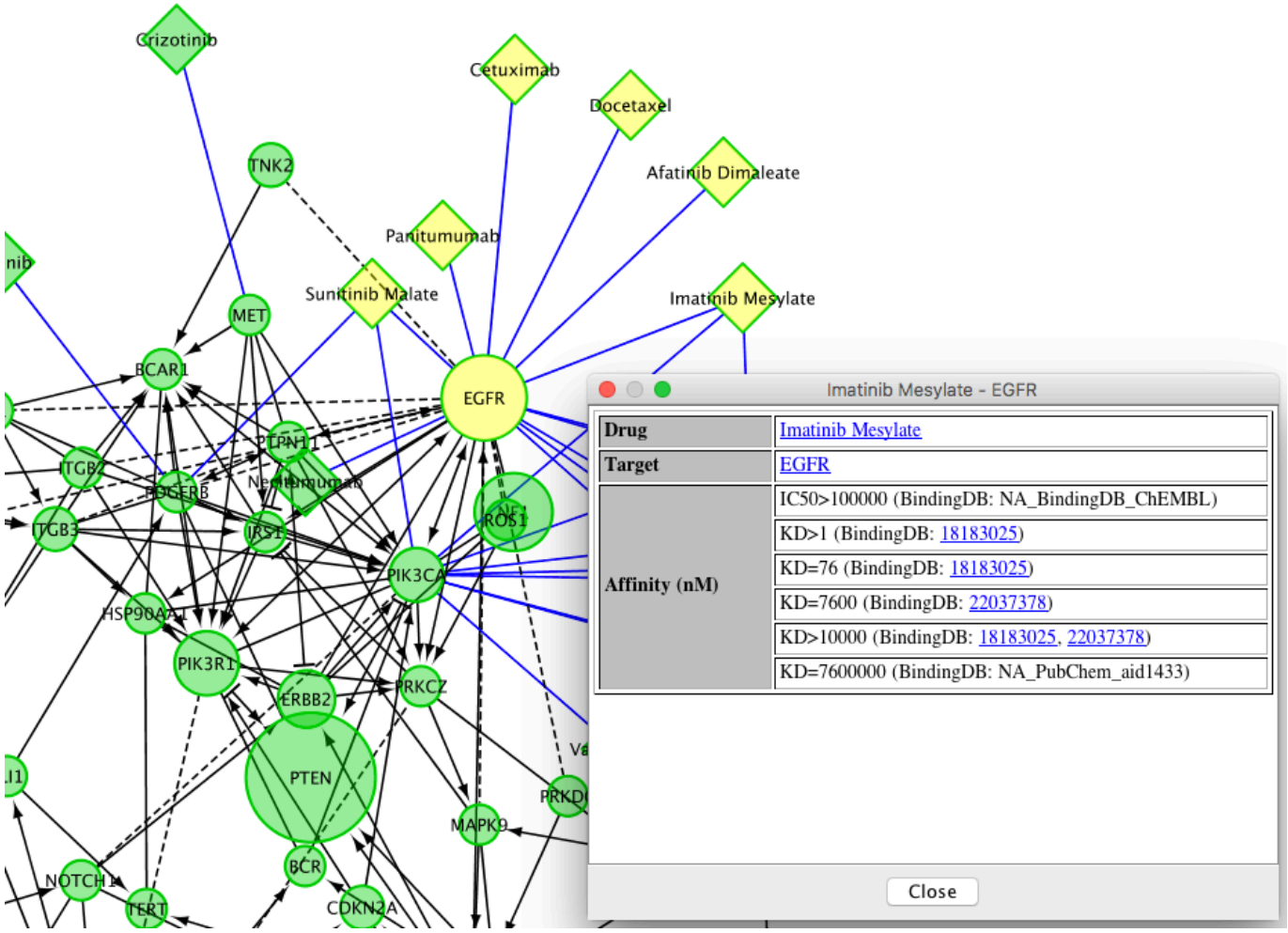
NYU Langone MEDICAL CENTER

OHSU

OICR

Guanming Wu

Visualize Cancer Targetome in the Reactome FI Network



TCGA GBM Mutation Profile

reactome

EMBL-EBI NYU Langone MEDICAL CENTER OHSU OICR

3) Pathway-Based Modeling

- Apply list of altered {genes, proteins, RNAs} to biological pathways.
- Preserve detailed biological relationships.
- Attempt to integrate multiple molecular alterations together to yield lists of altered pathway activities.
- Pathway modeling shades into Systems Biology

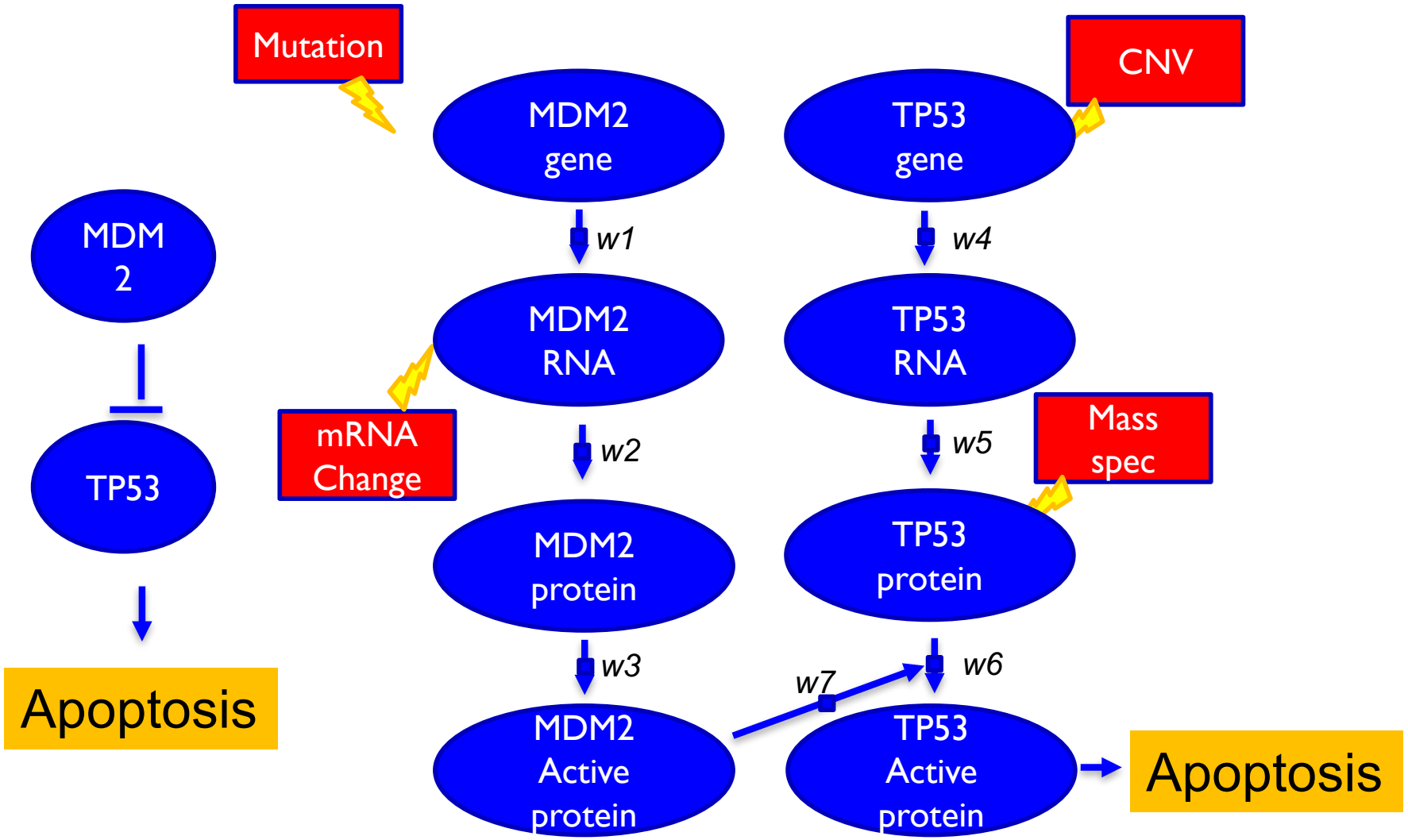
Types of Pathway-Based Modeling

- Partial differential equations/boolean models, e.g. CellNetAnalyzer
  - Mostly suited for biochemical systems (metabolomics)
- Network flow models, e.g. NetPhorest, NetworKIN
  - Mostly suited for kinase cascades (phosphorylation info)
- Transcriptional regulatory network-based reconstruction methods, e.g. ARACNe (expression arrays)
- Probabilistic graph models (PGMs), e.g. PARADIGM
  - Most general form of pathway modeling for cancer analysis at this time.

Probabilistic Graphical Model (PGM) based Pathway Analysis

- Attempt to integrate multiple molecular alterations together to yield lists of altered pathway activities.
  - Many omics data types available for one single patient
  - CNV, gene expression, methylation, somatic mutations, etc.
- Pathway and network-based Simulation
  - Find significantly impacted pathways for diseases
  - Link pathway activities to patient phenotypes
  - Predict drug effects: one drug or multiple drugs together?

PARADIGM

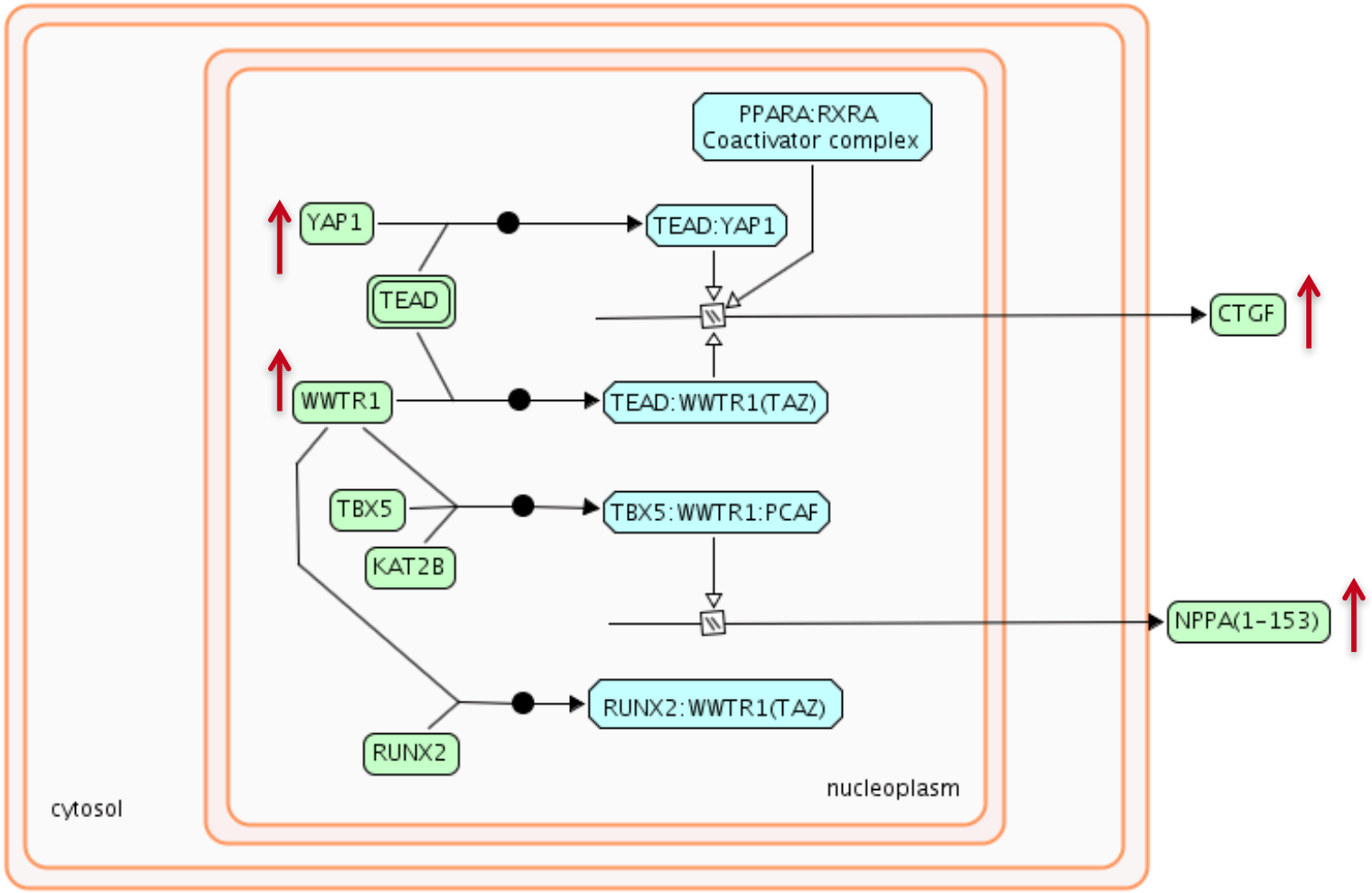


reactome

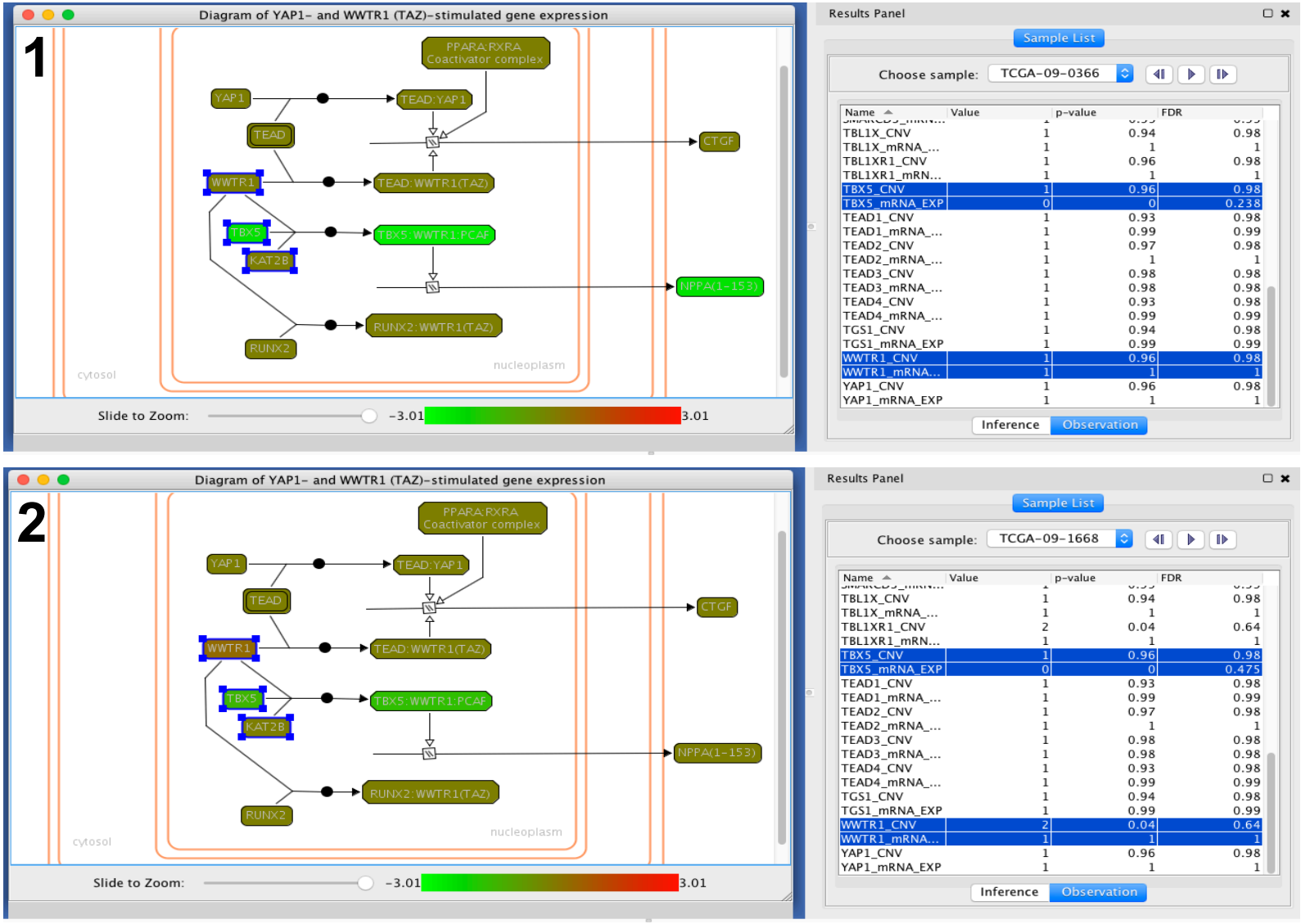
EMBL-EBI NYU Langone MEDICAL CENTER OHSU OICR

Adapted from Vaske, Benz *et al.* Bioinformatics 26:i237

Probabilistic Graphical Models (PGMs) for Reactome Pathways



PGM-based Single Patient Pathway View



reactome

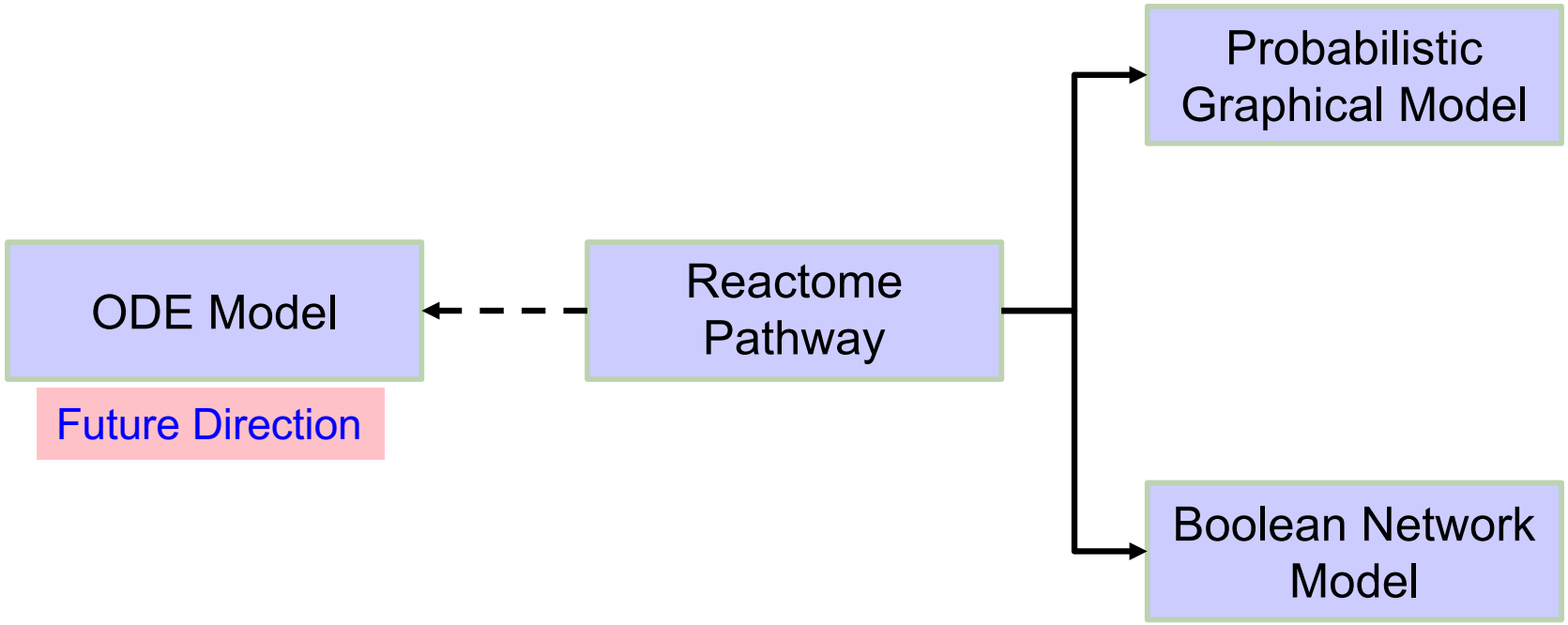
EMBL-EBI

NYU Langone MEDICAL CENTER

OHSU

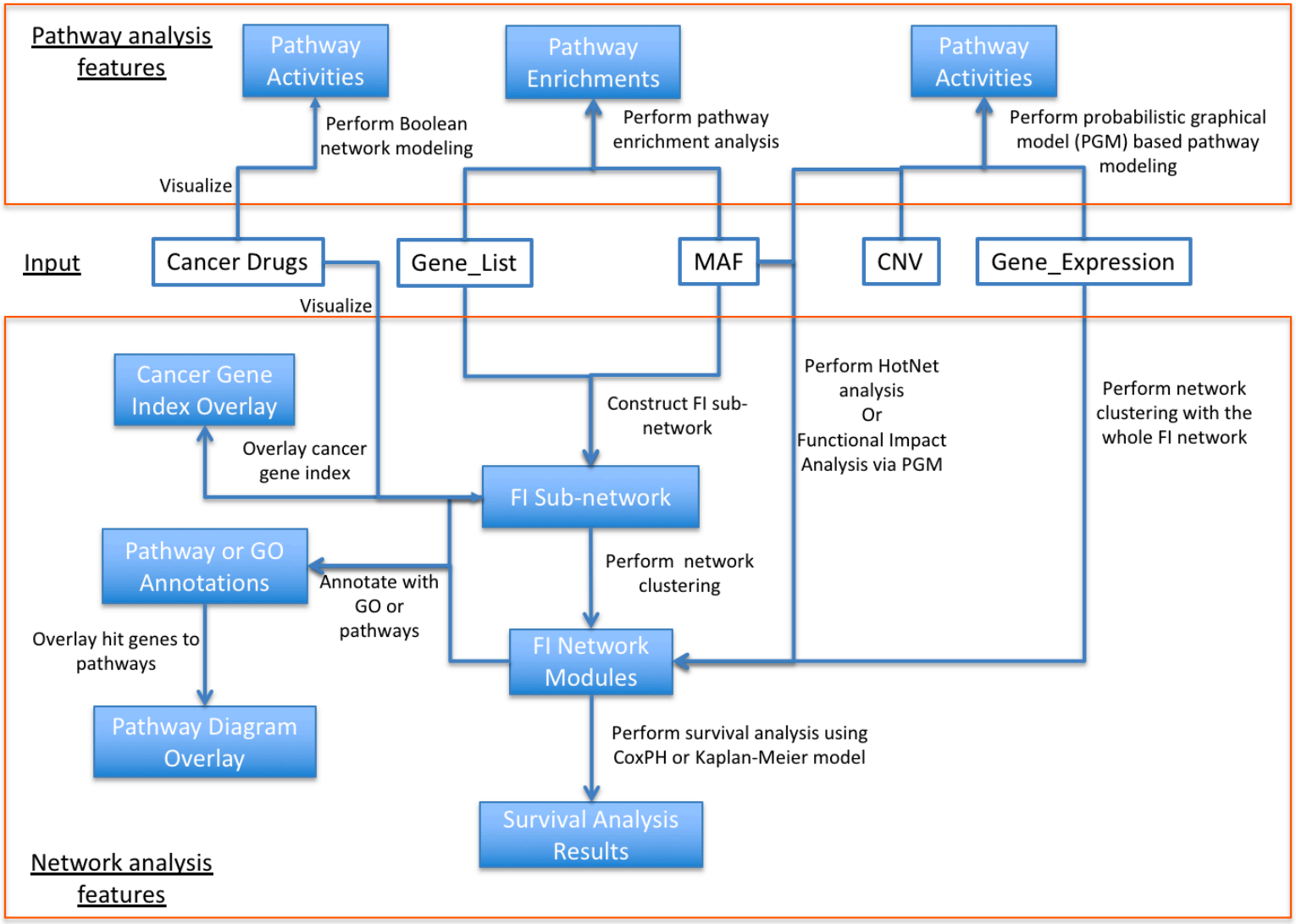
OICR

Building Quantitative Models for Reactome Pathways

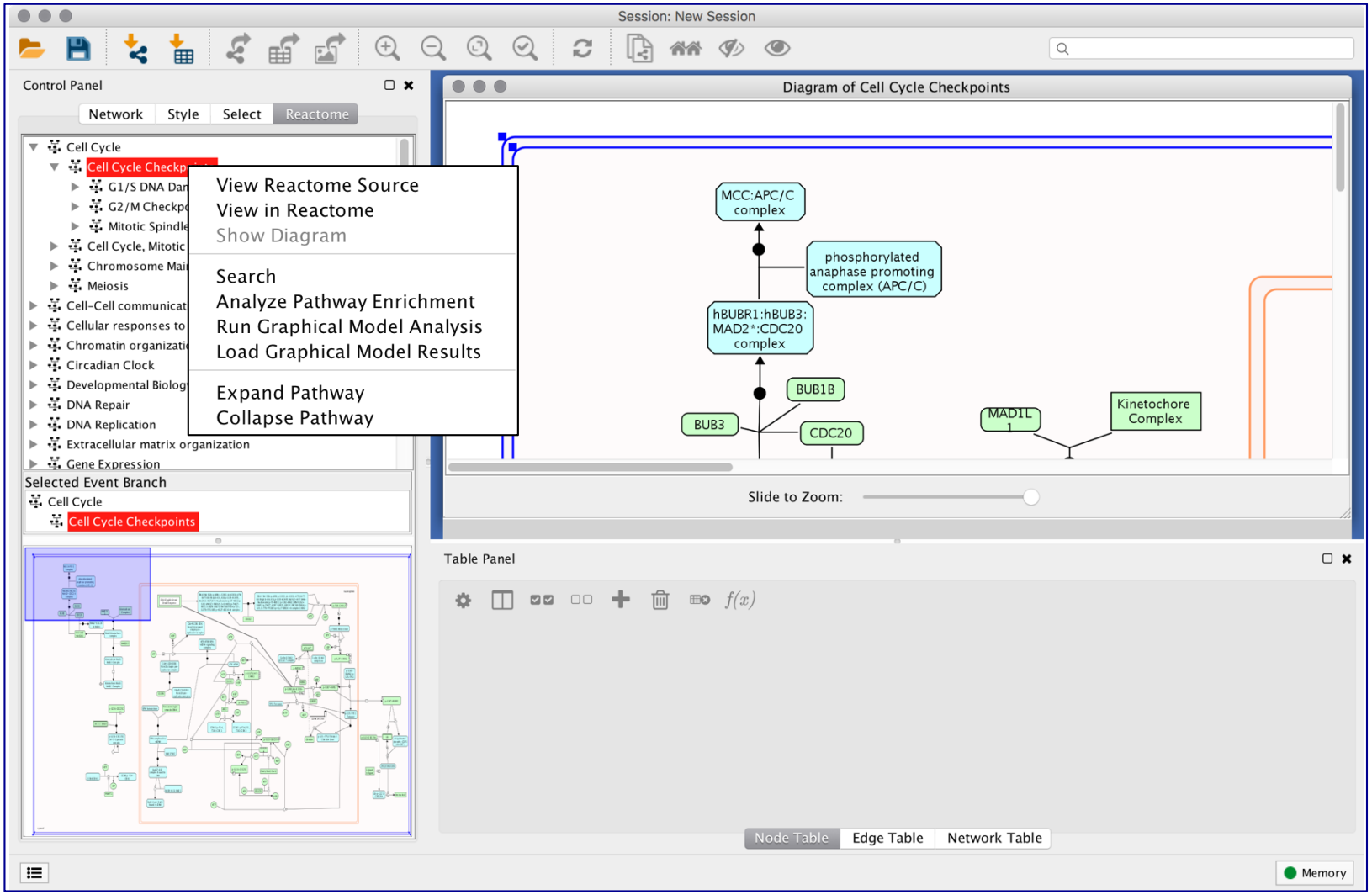


Tutorial

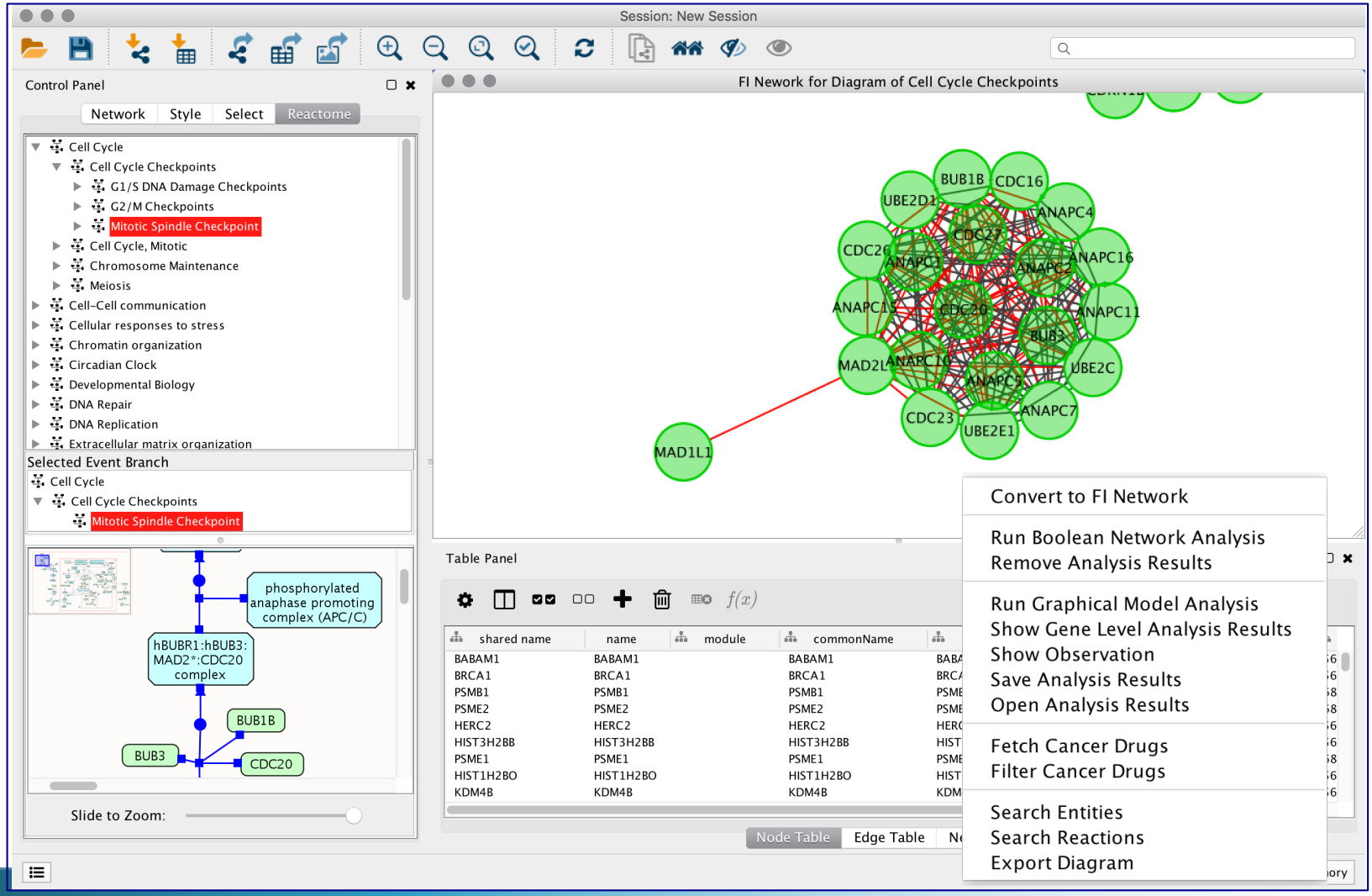
Major Features in ReactomeFIViz



A1) Reactome Pathway Enrichment Analysis



Displaying Reactome Pathways in the FI Network View



reactome

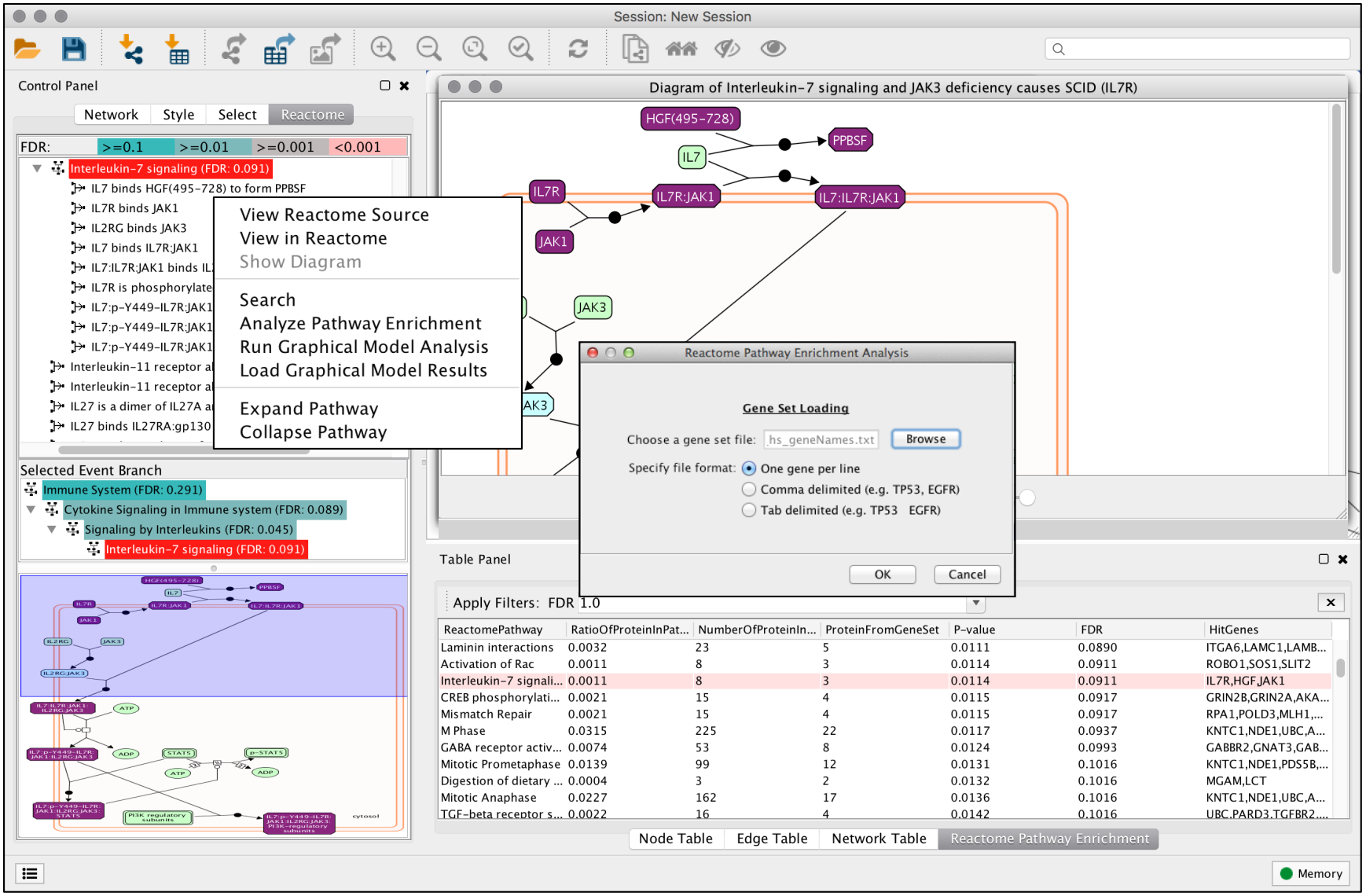
EMBL-EBI

NYU Langone MEDICAL CENTER

OHSU

OICR

Pathway Enrichment Analysis



reactome

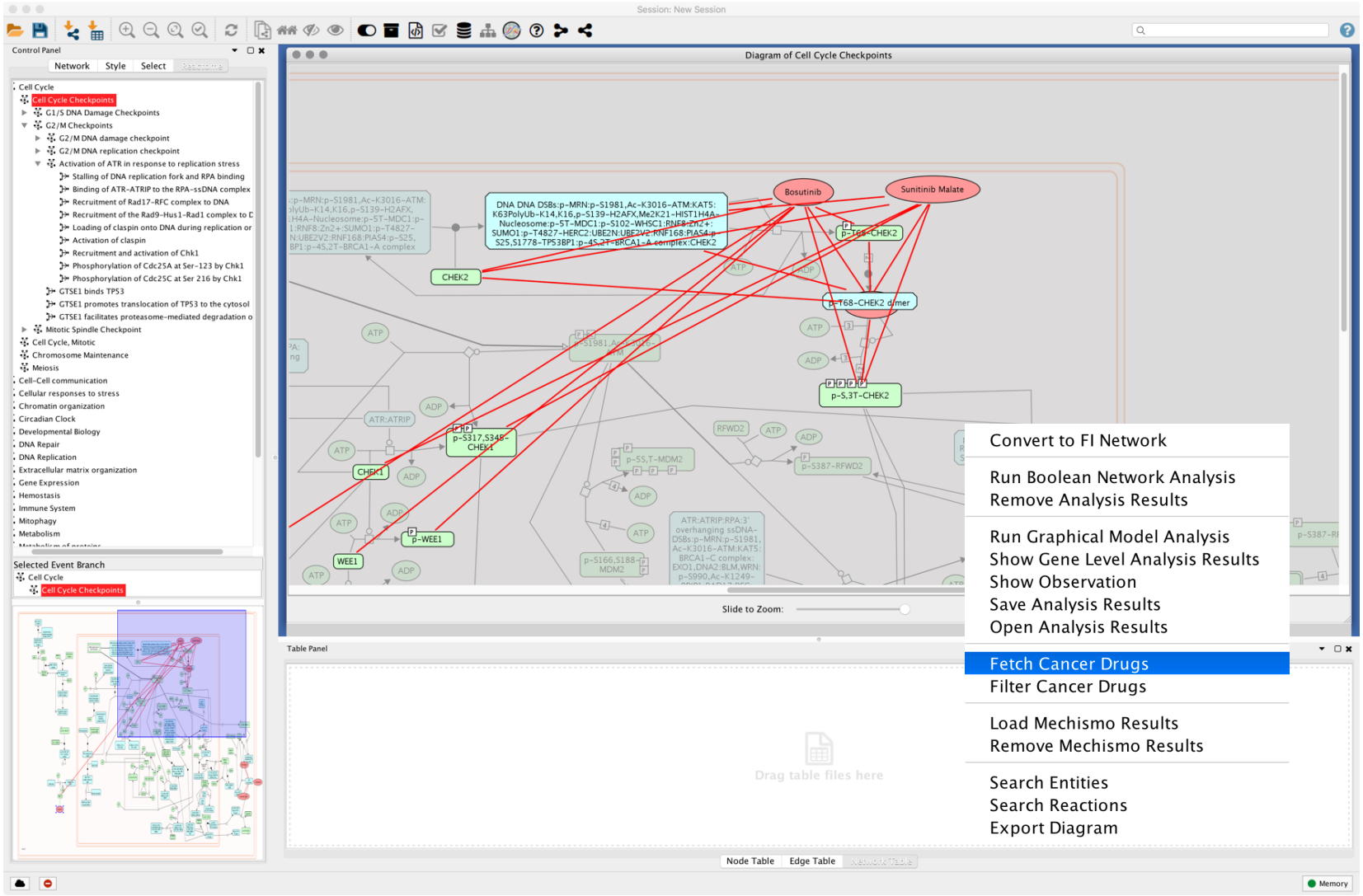
EMBL-EBI

NYU Langone MEDICAL CENTER

OHSU

OICR

Visualize Cancer Targetome in Reactome Pathways



reactome

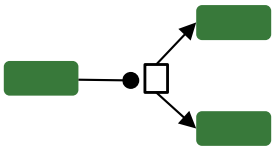
EMBL-EBI

NYU Langone MEDICAL CENTER

OHSU

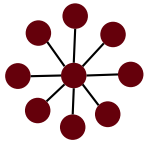
OICR

A2) De Novo Subnetwork Construction & Clustering



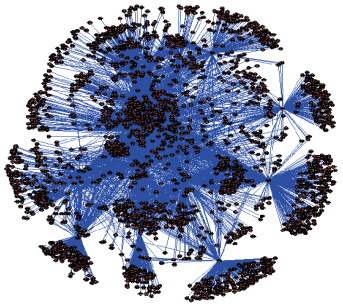
Curated Pathway DBs

+



Uncurated Interaction Evidence

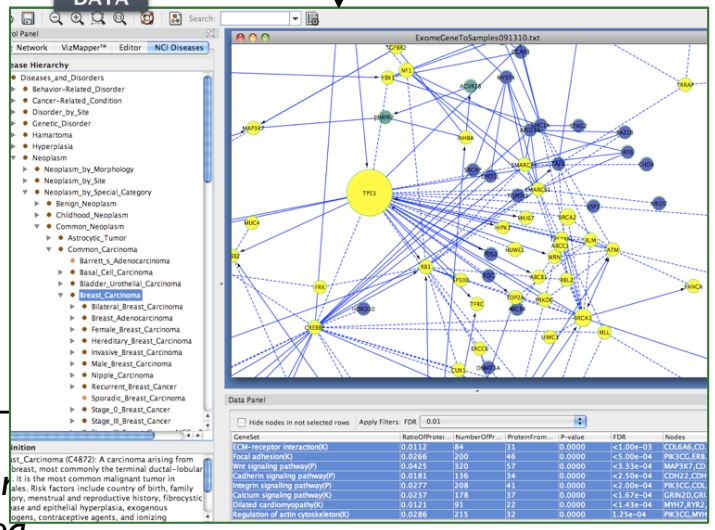
Machine Learning



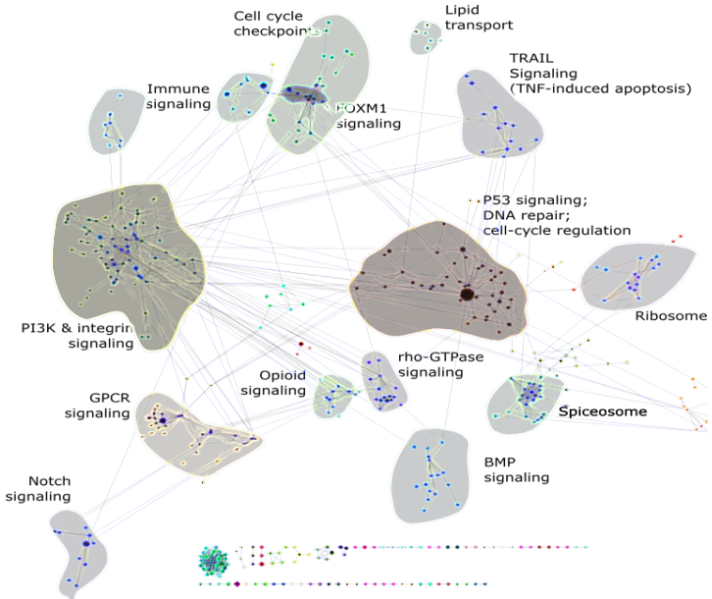
Reactome Functional Interaction Network
(~12K proteins; ~328K interactions)

+

Project your data into Reactome FI Network



Extract and Cluster and Annotate Altered Genes



Disease "modules" (10-30)

Cytoscape using ReactomeFIViz app

reactome

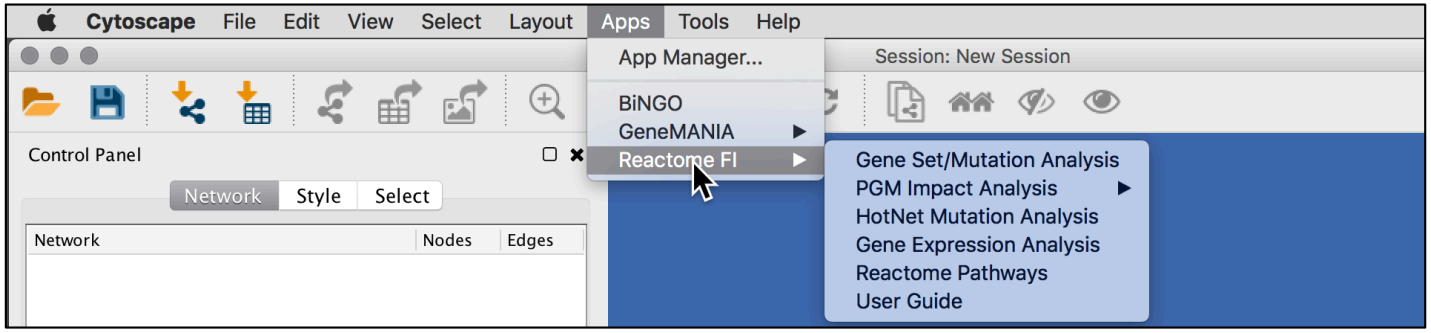
EMBL-EBI

NYU Langone MEDICAL CENTER

OHSU

OICR

Upload your data

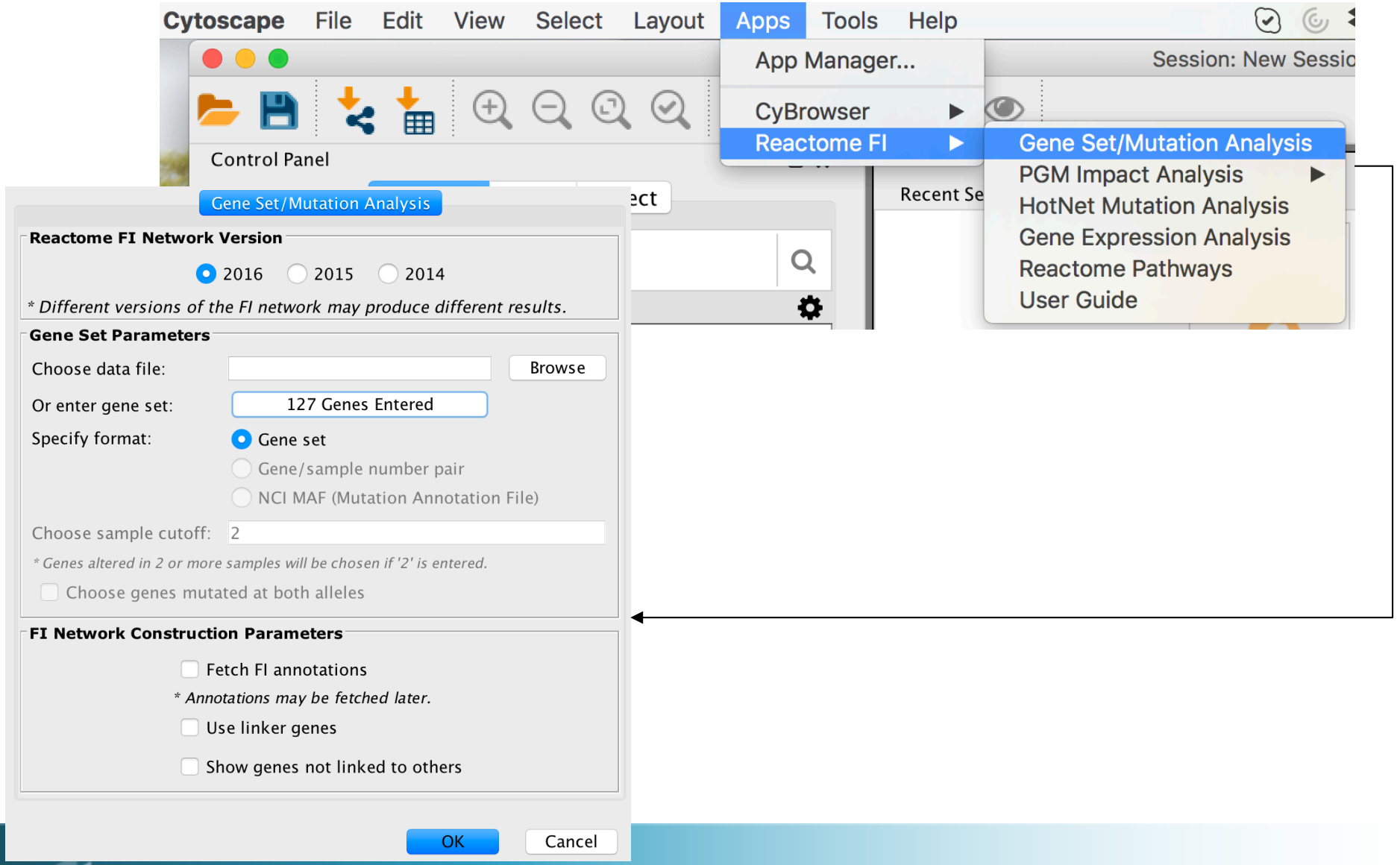


- FI plug-in supports four file formats:
  - Simple gene set: one line per gene
  - Gene/sample number pair. Contains two required columns, gene and number of samples having gene mutated, and an optional third column listing sample names (delimited by semi-colon ;)
  - NCI MAF (mutation annotation file)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

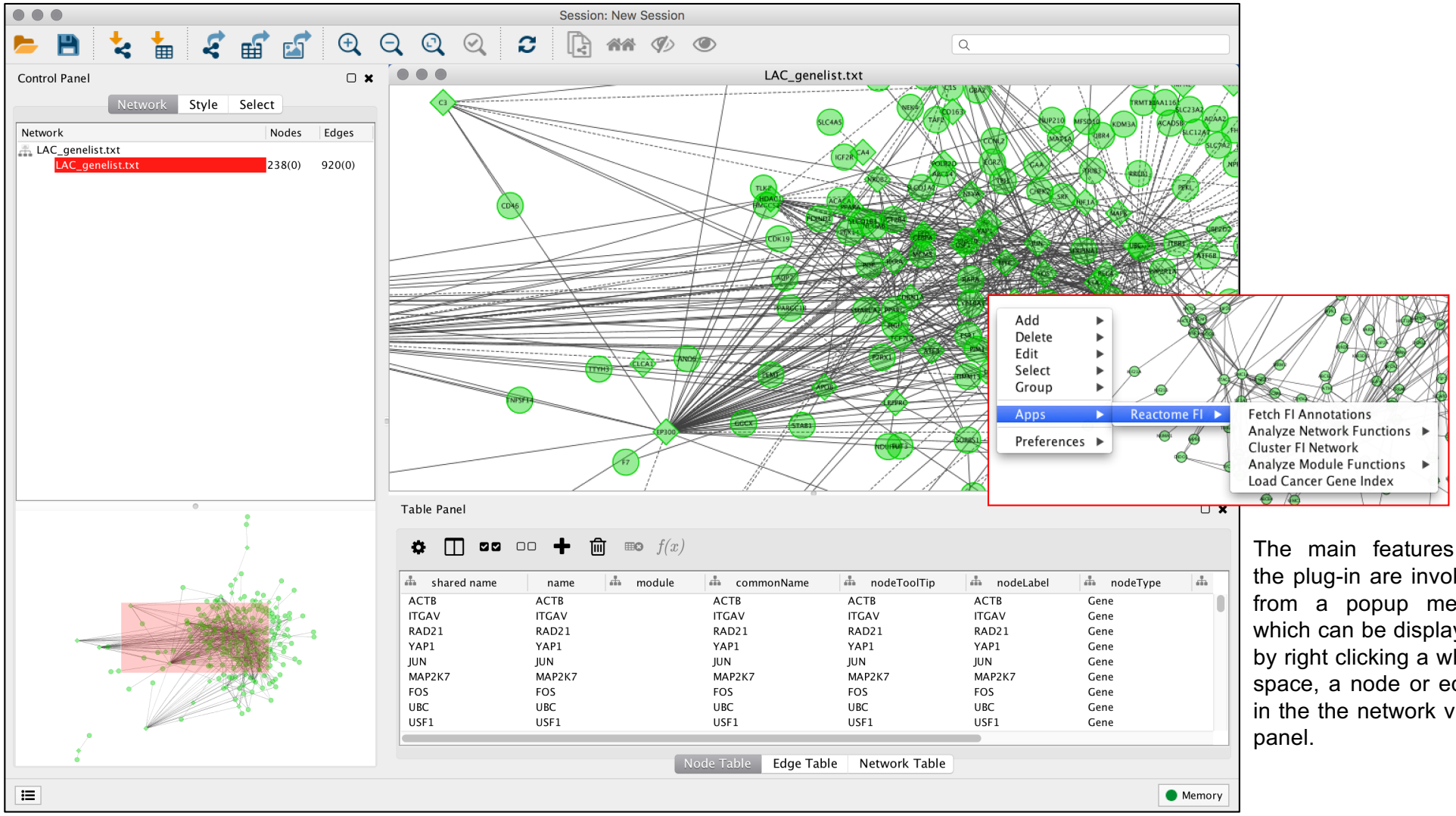
File Formats

- Choose Plugins, Reactome FIs.
- FI plug-in supports four file formats:
  - Gene list
  - Gene-Sample gene
  - NCI Mutation Annotation File
  - Microarray Expression Data

Gene Set-based Analysis



FI Results Display



The main features of the plug-in are invoked from a popup menu, which can be displayed by right clicking a white space, a node or edge in the the network view panel.

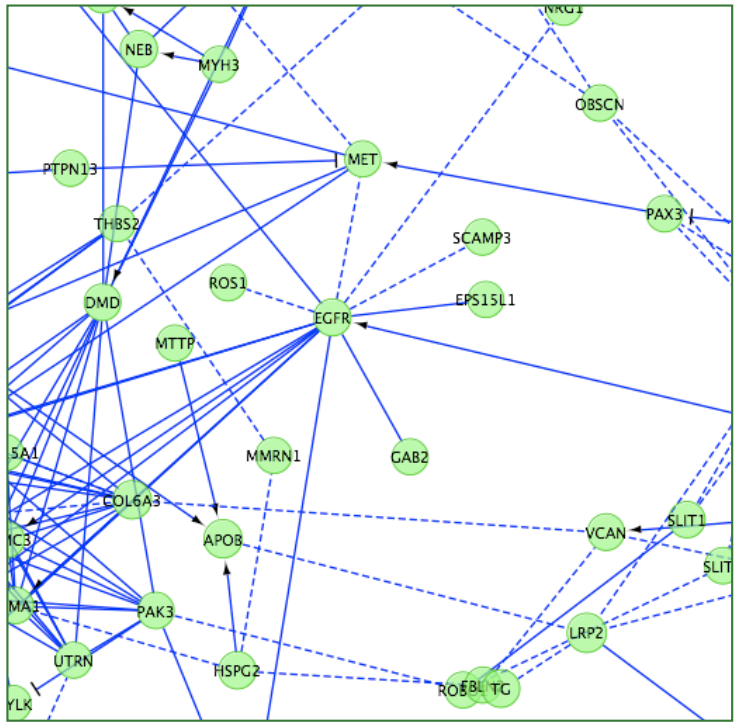
- Constructed network is displayed in the Network View panel using an FI specific visual style

reactome

EMBL-EBI NYU Langone MEDICAL CENTER OHSU OICR

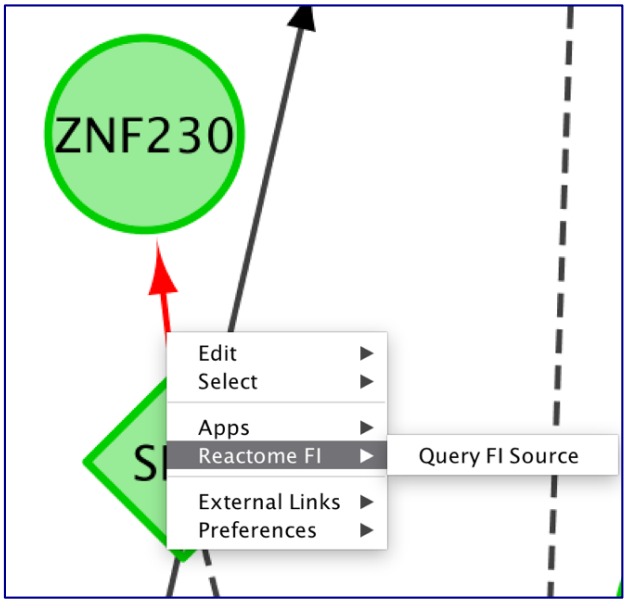
FI Annotations

- 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.

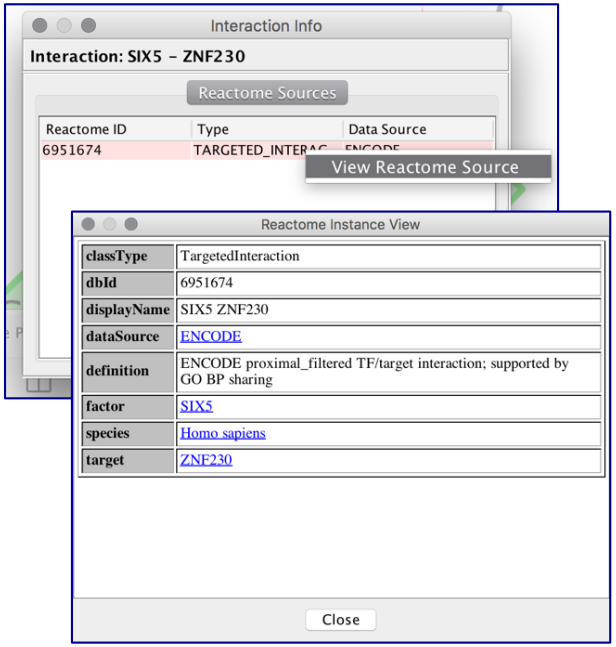


The main features of the plug-in are invoked from a popup menu, which can be displayed by right clicking a node or edge in the the network view panel.

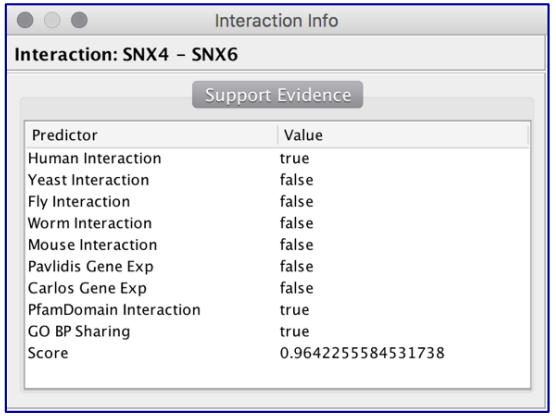
Query FI Source



Annotated FIs

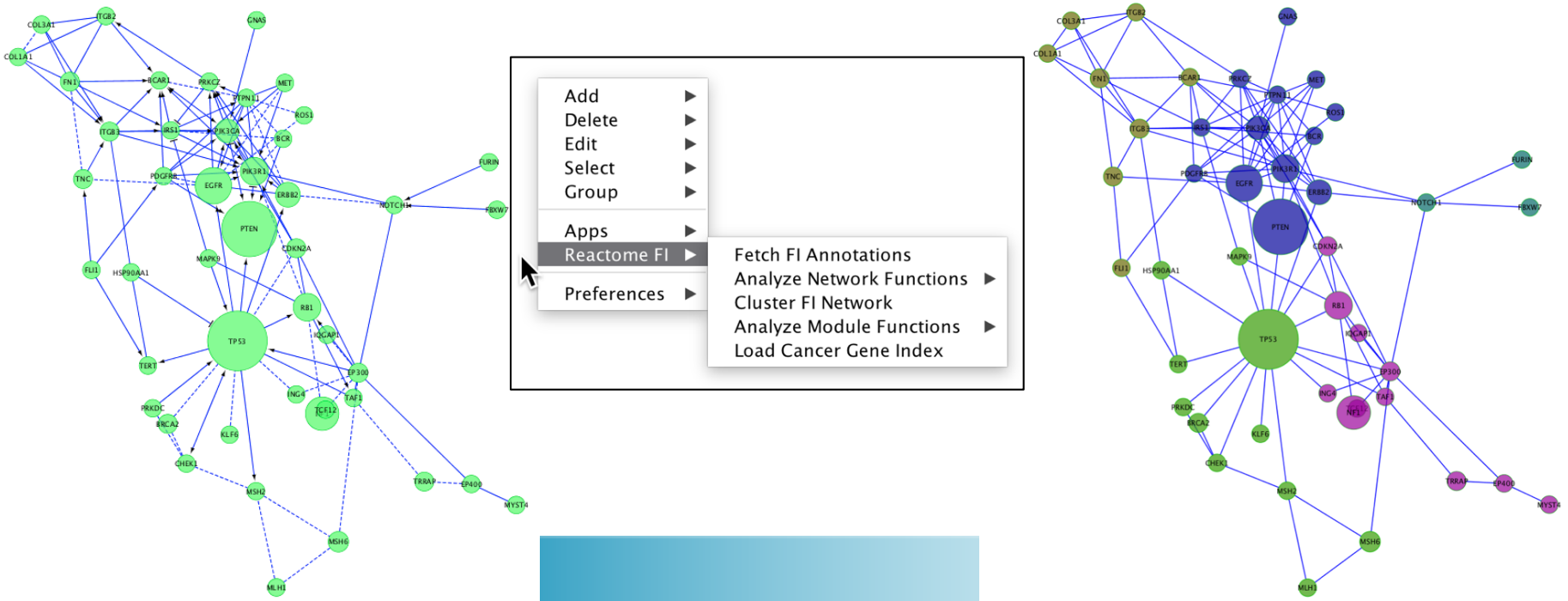


Predicted FIs



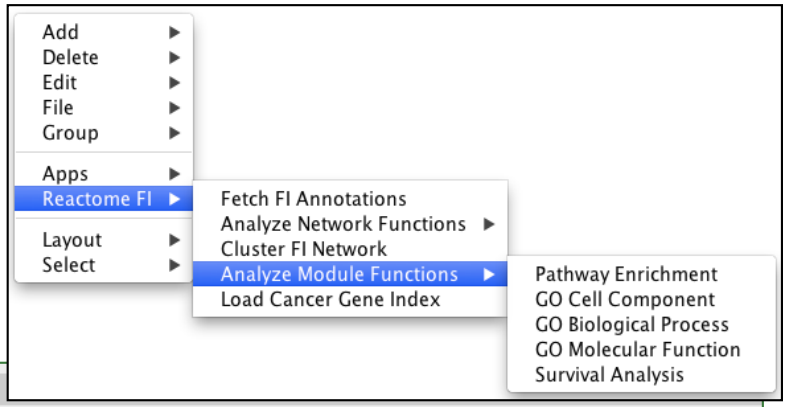
Cluster FI Network

- 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 modules
  - Filter by FDR



Data Panel

Hide nodes in not selected rows | Apply Filters: FDR 0.01 | Module Size 10

0.0010, 0.0050, ✓ 0.01, 0.05, 0.25, 0.5, 1.0

15, 13, 12, 11, ✓ 10, 9, 8, 7

Module	GeneSet	RatioOfProteinIn		mModule			Nodes
0	Translation(R)	0.0158					RPL18,RPL17,RPL36...
0	Influenza Life Cycle(R)	0.0249					RPL18,RPL17,RPL36...
0	Ribosome(K)	0.0117					RPL18,RPL17,RPL36...
0	Metabolism of protei...	0.0267					RPL18,RPL17,RPL36...
1	M Phase(R)	0.0128					ITGB3BP,MAD1L1,CC...
1	Aurora B signaling(N)	0.0052					AURKC,AURKB,CDCA...
1	Signaling by Aurora k...	0.0125					AURKC,AURKB,CDCA...
2	Glucose Regulation of...	0.0197	148	16			NDUFB4,NDUFA2,ND...
2	Parkinson's disease(K)	0.0176	132	15	0.0000	<1.67e-04	NDUFB4,NDUFA2,ND...
2	Alzheimer's disease(K)	0.0223	168	15	0.0000	<1.67e-04	NDUFB4,NDUFA2,ND...
2	Huntington's disease(K)	0.0246	185	15	0.0000	<1.67e-04	NDUFB4,NDUFA2,ND...
2	Oxidative phosphoryl...	0.0178	134	15	0.0000	<1.67e-04	NDUFB4,NDUFA2,ND...
2	Electron Transport C...	0.0101	76	16	0.0000	<1.67e-04	NDUFB4,NDUFA2,ND...
2	Metabolic pathways(K)	0.1489	1120	16	0.0000	<1.43e-04	NDUFB4,NDUFA2,ND...
3	Antigen processing a...	0.0104	78	9	0.0000	<1.00e-03	KLRC2,KIR2DS1,HLA...
3	Immunoregulatory int...	0.0153	115	8	0.0000	<5.00e-04	KIR2DS1,HLA-B,HLA...
3	Natural killer cell me...	0.0182	137	7	0.0000	<3.33e-04	KLRC2,KIR2DS1,HLA...

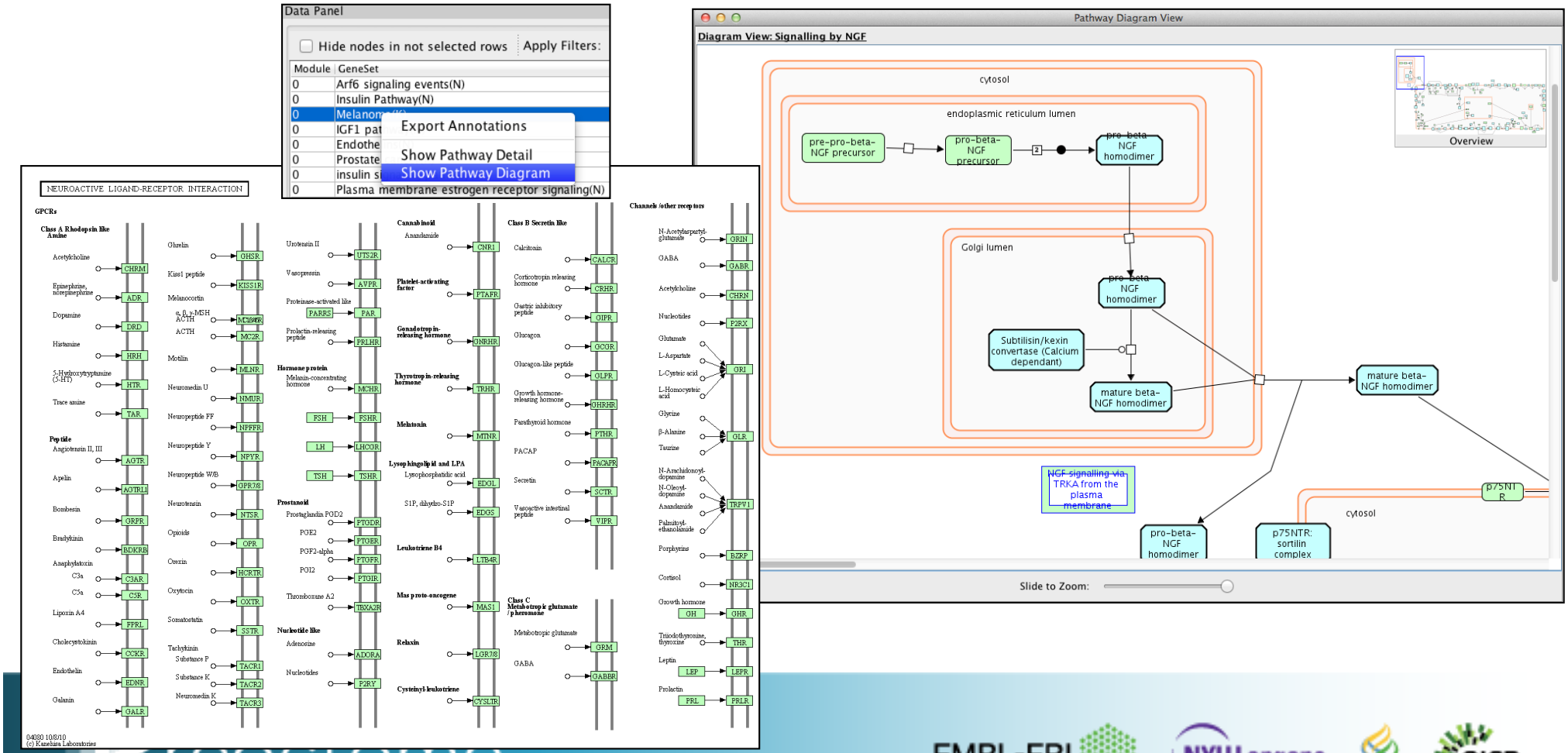
Node Attribute Browser | Edge Attribute Browser | Network Attribute Browser | MCL Module Browser | Pathways in Modules

reactome

EMBL-EBI NYU Langone MEDICAL CENTER OHSU OICR

Other Features – Show Pathway Diagrams

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



reactome

EMBL-EBI

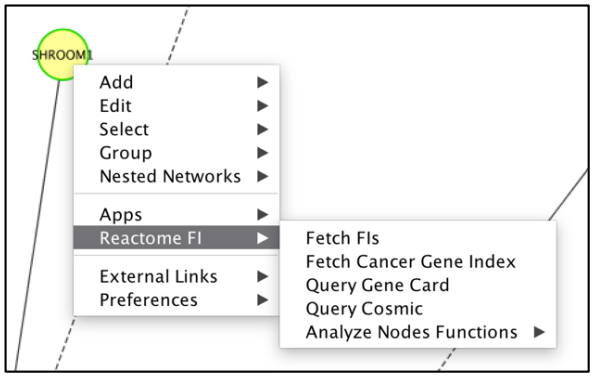
NYU Langone MEDICAL CENTER

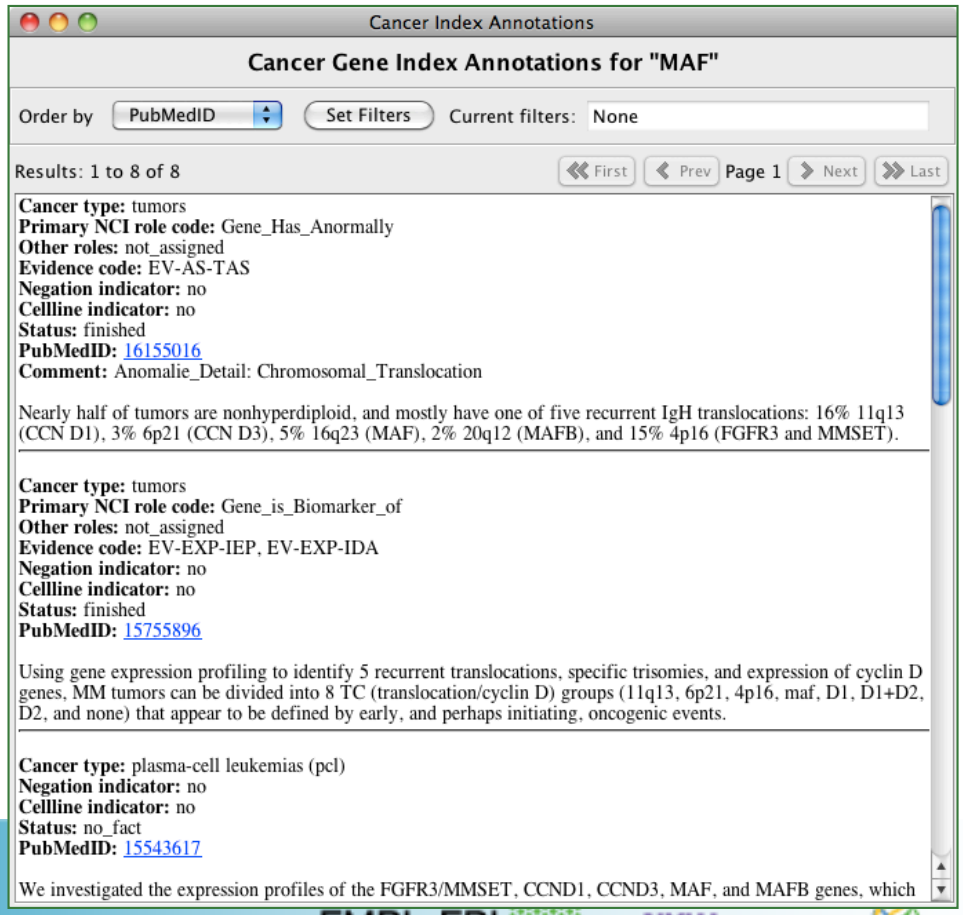
OHSU

OICR

Other Features – NCI Cancer Gene Index

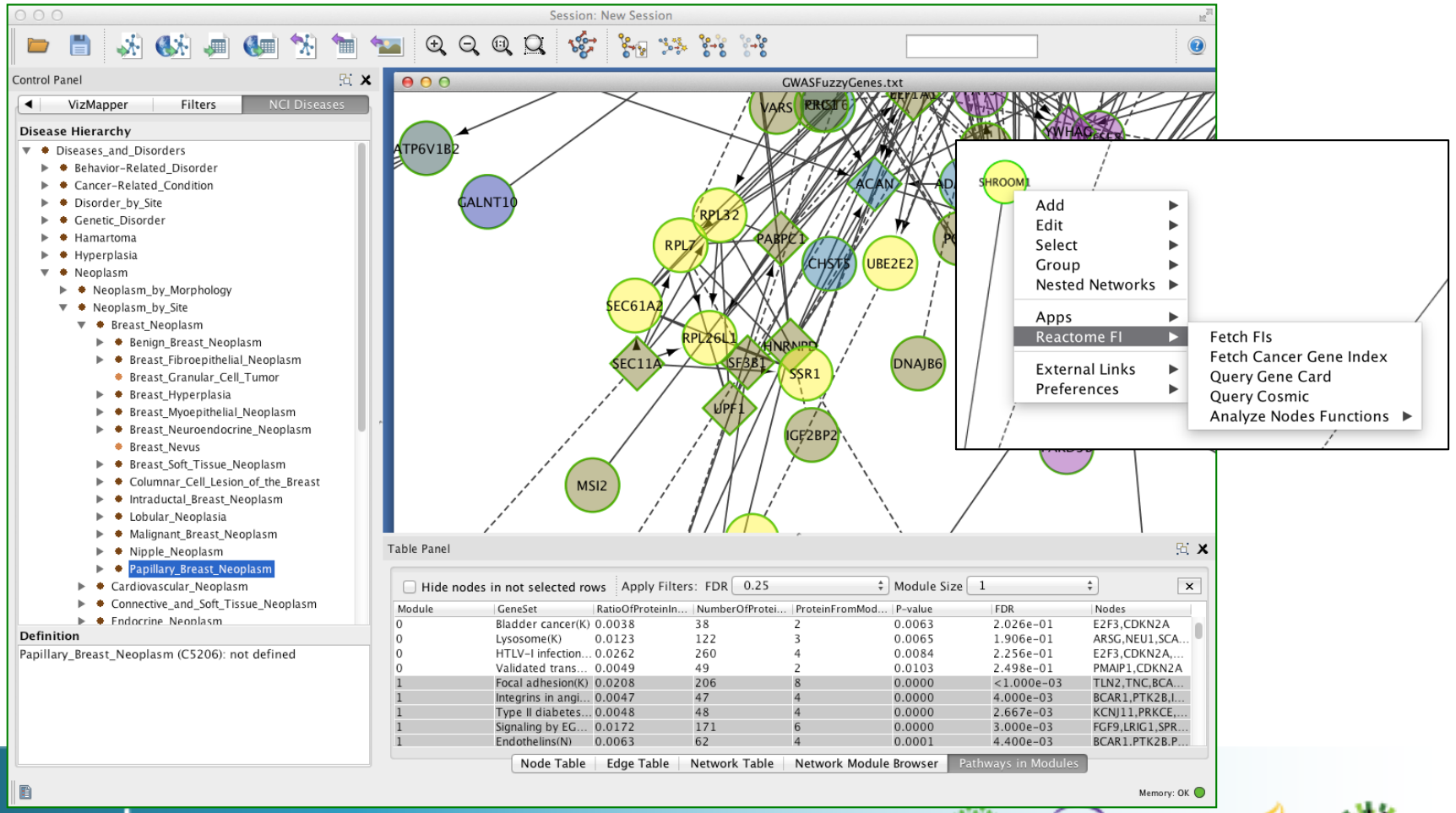
- View detailed annotations for the selected gene or protein.
- Annotations are sortable by PubMed ID, Cancer type, status, and other criteria.





Other Features – 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.



reactome

EMBL-EBI

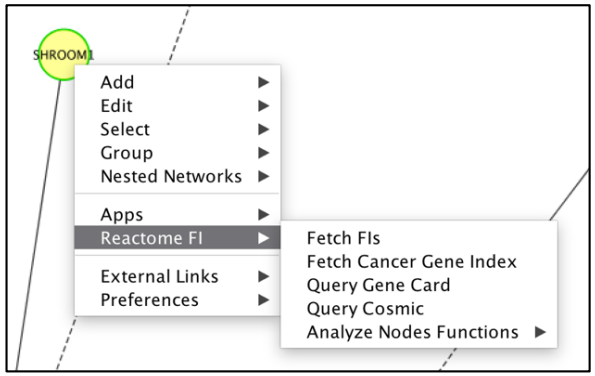
NYU Langone MEDICAL CENTER

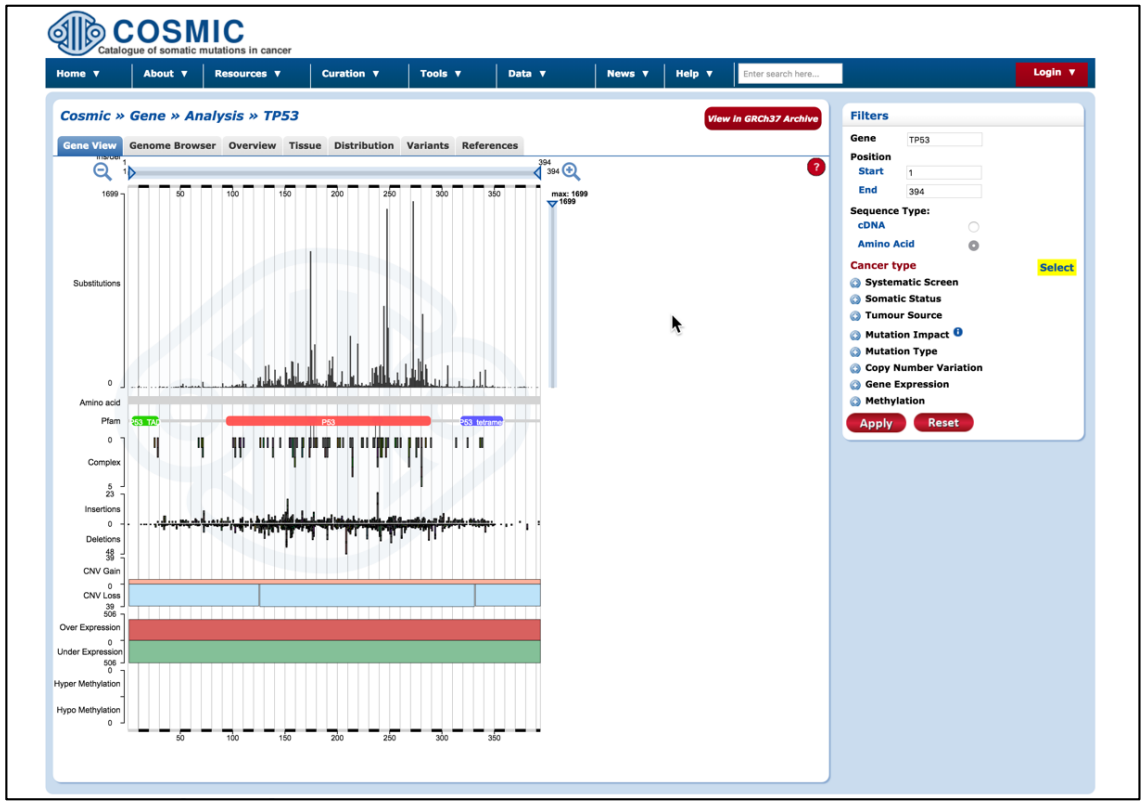
OHSU

OICR

Other Features – COSMIC

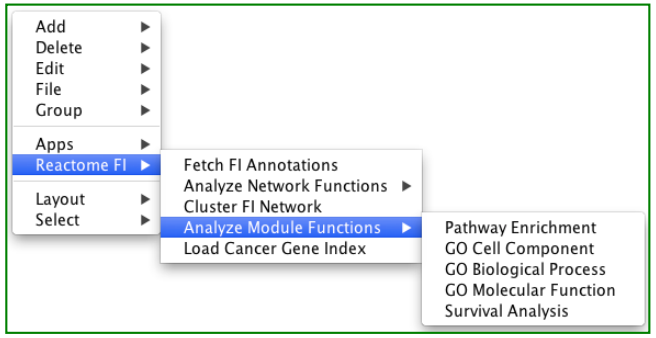
- View detailed variant annotations for the selected gene or protein from COSMIC database.

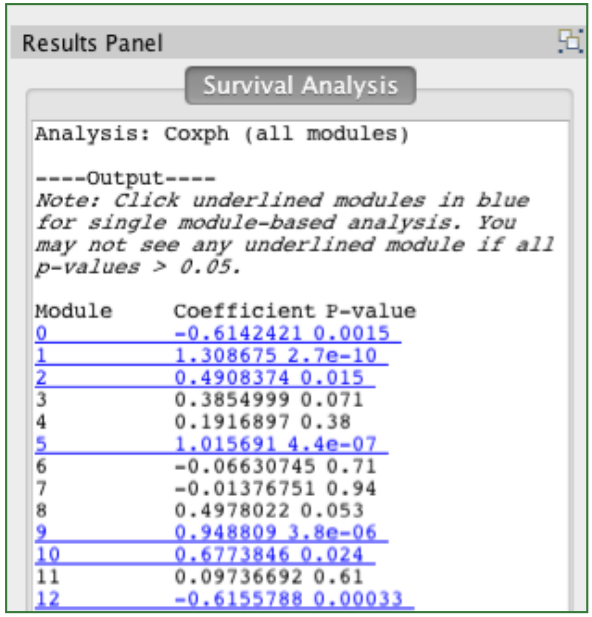


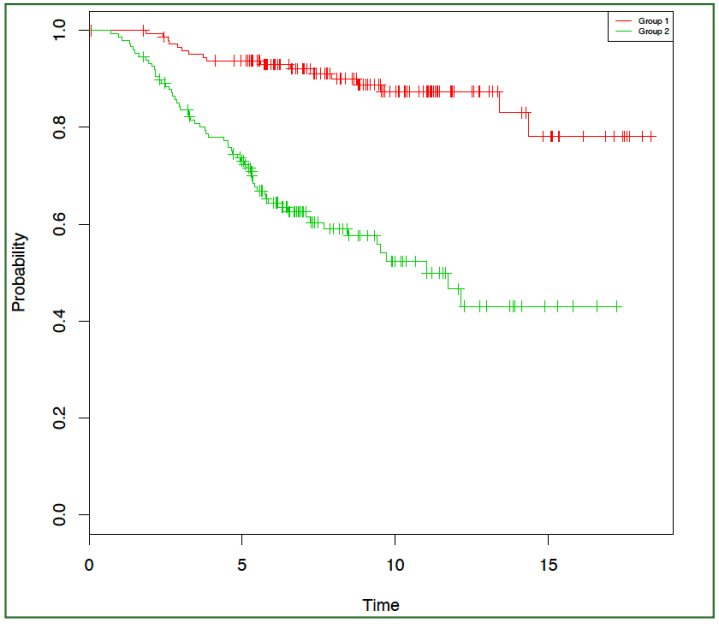


Module Based Survival Analysis

- 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.







reactome EMBL-EBI NYU Langone MEDICAL CENTER OHSU OICR

For any questions or feedback, please contact
help@reactome.org