[회사 이름 입력]

cMapper Documentation

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cMapper User Queries

In the following supplementary tables we have presented details about queries that we inputted to the cMapper for generation of figure 1 to 3. Readers can use the information given in the following tables to regenerate the similar graphs as given in the paper.

Table S1: User Input query for Figure 1

Input Type	**Input**			
Gene	CTNNB1; STAT3; FGF19			
Databases Included	Associated Genes, UniProt, Expression Atlas, REACTOME, ChEMBL, BioModels, BioSamples			
Databases Excluded	None			
Filters				
Organism Filter	**Organ Filter**	**Pathway Filter**	**Graph Type**	**Output Type**
Homo Sapiens	All Organs	All Pathways	All Connections	View Graph

Table S2: User Input query for Figure 2

Input Type	**Input**			
Gene	CTNNB1; STAT3; FGF19			
Databases Included	UniProt, Expression Atlas, REACTOME, ChEMBL, BioModels, BioSamples			
Databases Excluded	Associated Genes			
Filters				
Organism Filter	**Organ Filter**	**Pathway Filter**	**Graph Type**	**Output Type**
All Organisms	All Organs	All Pathways	Shared Connections	View Graph

Table S3: User Input query for Figure 3

Input Type	**Input**			
Gene	CTNNB1; STAT3; FGF19			
Databases Included	Associated Genes			
Databases Excluded	UniProt, Expression Atlas, REACTOME, ChEMBL, BioModels, BioSamples			
Filters				
Organism Filter	**Organ Filter**	**Pathway Filter**	**Graph Type**	**Output Type**
All Organisms	All Organs	Metabolic Pathways	Shared Connections	View Graph

cMapper User Guide

The cMapper home page is very similar to any other search engine home page that provides users a state forward view to input genes or small molecules and select the filters for the graph generation. Figure S1 and S1A show the cMapper homepage which consists of filters, gene or small molecule selector, database selector and input text box.

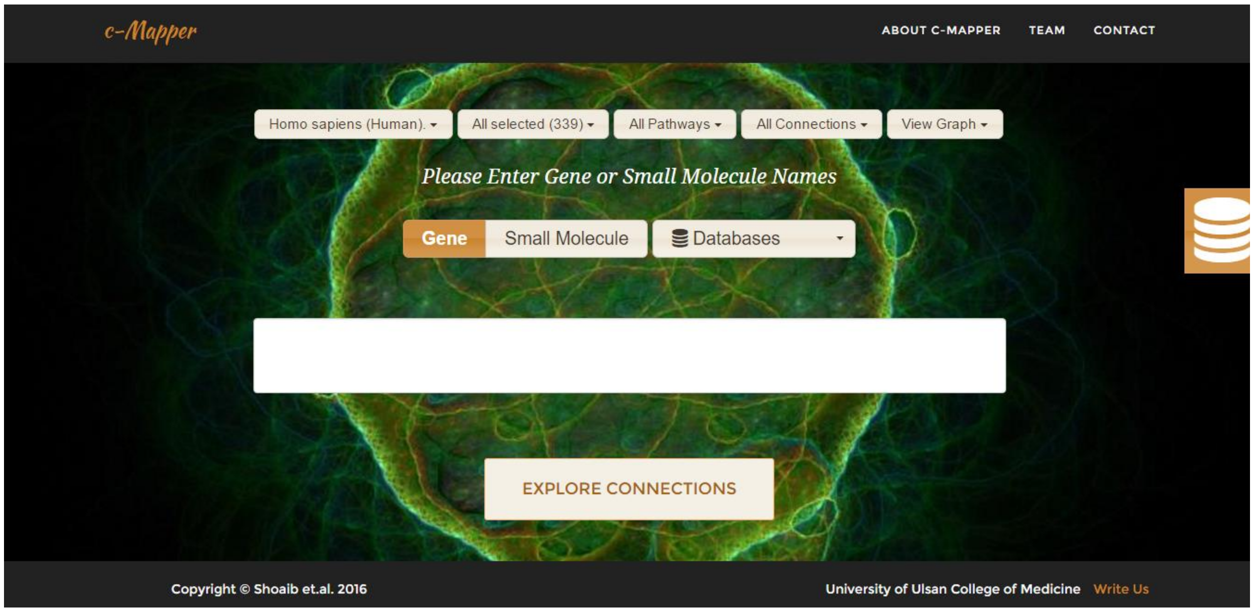


Figure S1: cMapper Homepage.

When a user enters list of genes of small molecules the output of cMapper is a graph. Figure S2 shows the cMapper graph displaying window. On the top the list of genes or small molecules that had contributed towards creation of graph are sown. In the middle of the screen the graph and bottom is general footer.

User can edit the list of genes by clicking on the “edit” button and download the graph by clicking on the “download” button. Upon selecting the edit option, a screen similar to figure S3 appears which allow users to alter the list of genes or small molecule as well as the filtering options. Furthermore, figure S4, S5 and S6 show the screen short of filtering options

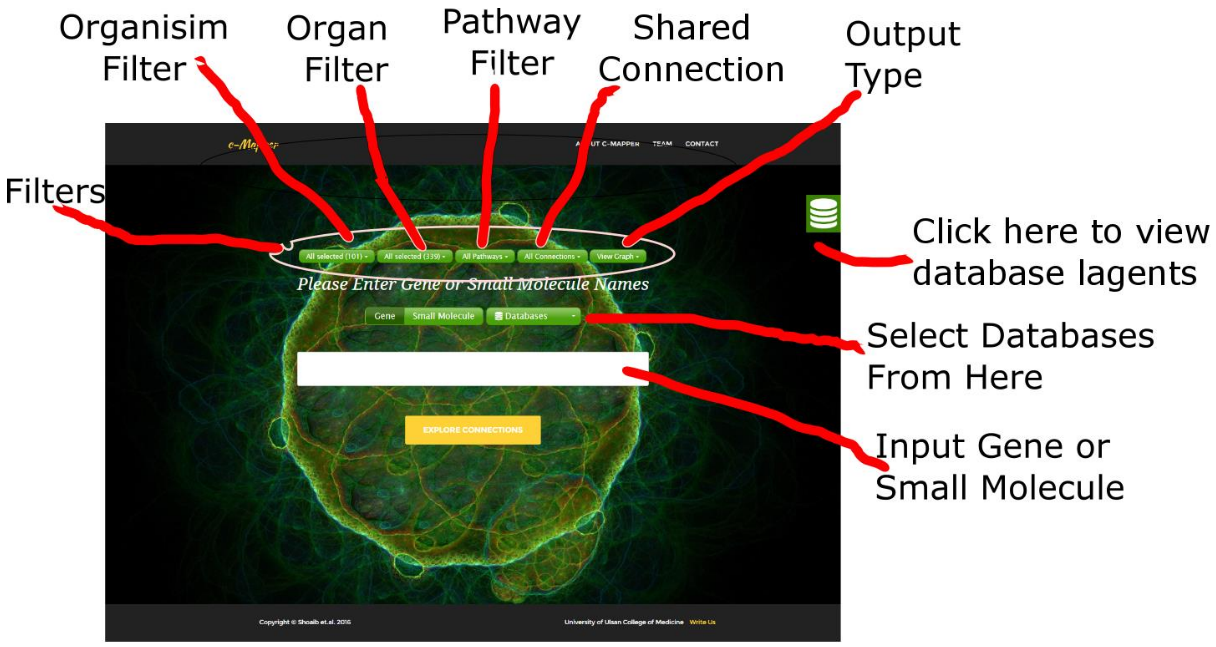


Figure S1A: Components of cMapper Tool

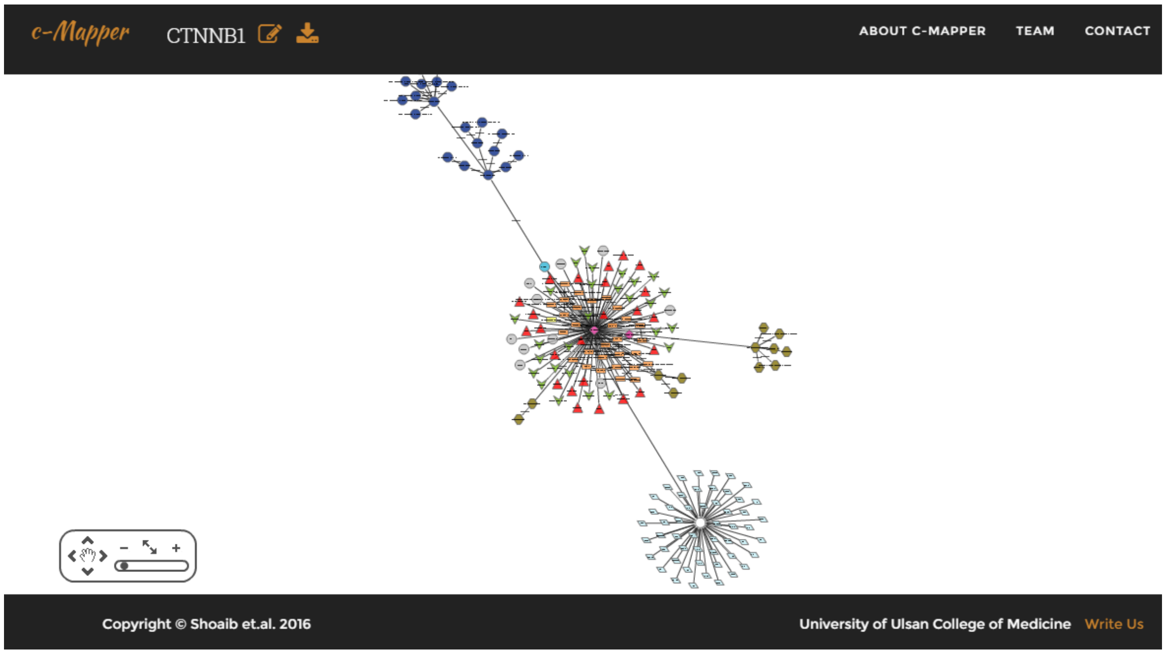

c-Mapper
CTNNB1
ABOUT C-MAPPER
TEAM
CONTACT
Copyright © Shoaib et.al. 2016
University of Ulsan College of Medicine
Write Us

Figure S2 cMapper output windows which includes list of gene names – "CTNNB1" in this case –, edit button, and download button. The "edit" button can be used to edit list of gene names or update filters whereas "download" button can be used to download the graph as PNG file.

1 Graph FIlters

In the following we have shown the details about filters andtheir functions along with screen short for each filter.

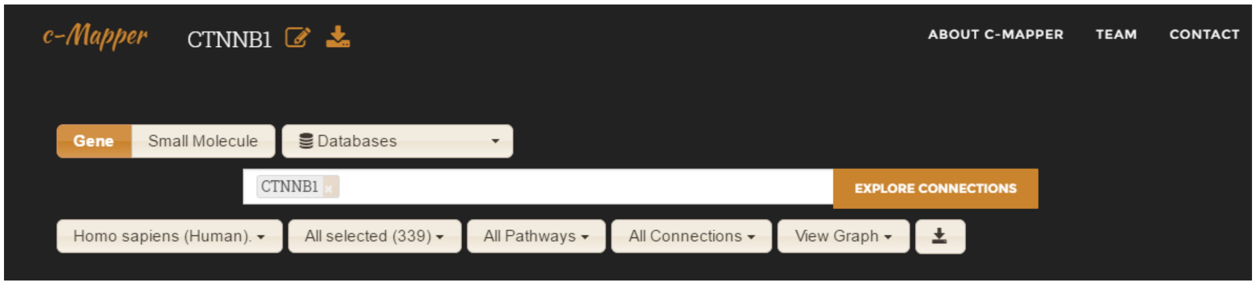


Figure S3: cMapper editing window that appears after clicking the edit button.

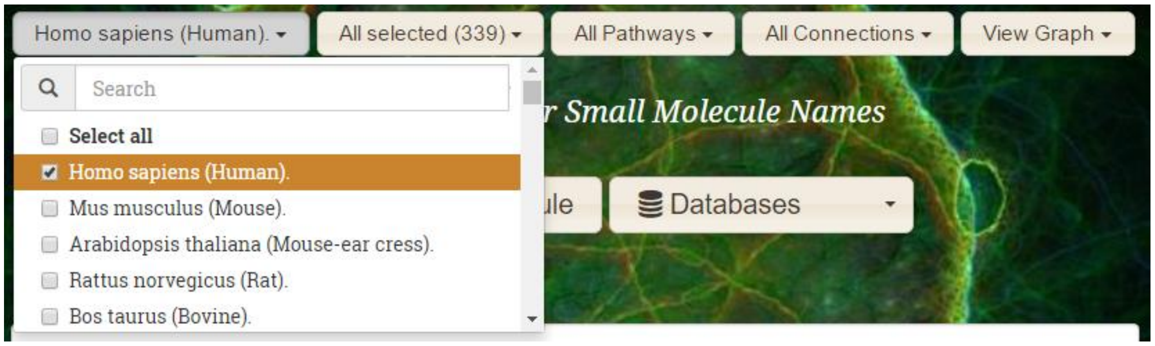


Figure S4: cMapper organismic filter. By default Homo sapiens (Human) organism is selected users can edit and select multiple organisms of their choices. The list is sorted based on number of proteins against organisms in the UniProt KB.

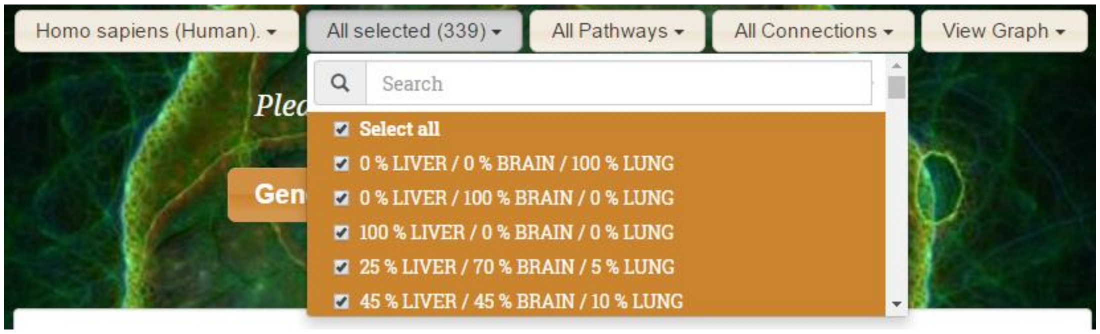

Homo sapiens (Human).
All selected (339)
All Pathways
All Connections
View Graph
Search
Select all
0 % LIVER / 0 % BRAIN / 100 % LUNG
0 % LIVER / 100 % BRAIN / 0 % LUNG
100 % LIVER / 0 % BRAIN / 0 % LUNG
25 % LIVER / 70 % BRAIN / 5 % LUNG
45 % LIVER / 45 % BRAIN / 10 % LUNG
Plea
Gen

Figure S5: cMapper Organ selector that users can use to specify the list of organs like “brain”, “liver” etc. This list is sorted based on Alpha-numeric letters. By default all organs are selected users can unselect organs of their choice as well.

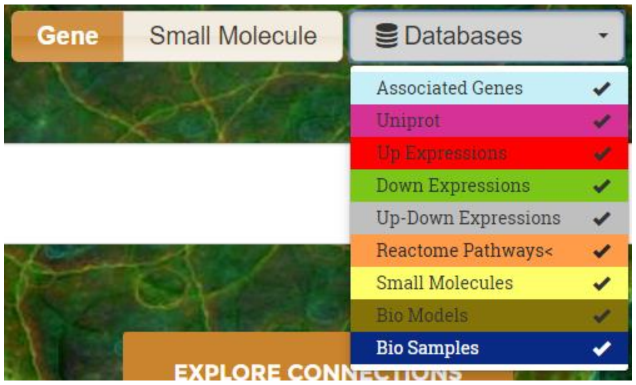
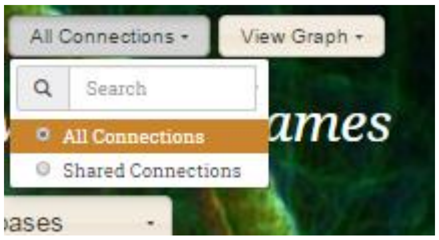
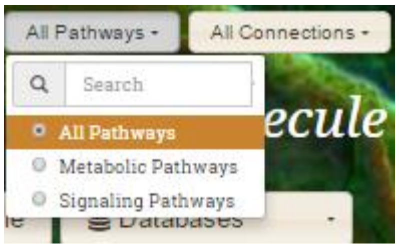


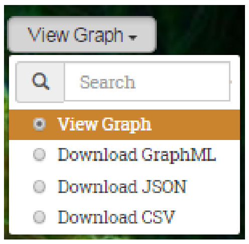
Figure S6: cMapper database selector that allows the users to select the database of their choice. When a user deselected a database the output graph will not contain the database entities from the deselected database.



All and shared connections filter



Metabolic and Signaling pathway filter



Output Option

Similarly other filter includes (1) “Metabolic” and “Signaling” pathways filter, (2) “All” and “Shared Connections”.

2 Output Options:

cMapper allows users to select their output type. These output types are

- View graph: displays the graph on the user’s screen
- Download GraphML: downloads the user’s device in the GraphML format–,
- Download JSON: option downloads the user’s device as JSON Array–,
- Download CSV: downloads information about graph nodes and edges to the user’s machine in CSV format.

3 Downloading Graph as Image:

In order to save graph as PDF or PNG user may click PDF or Download Button after graph is displayed on the screen.

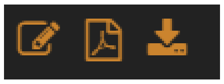


Figure S7: (left right) (1) Edit input, (2) Download PDF and (3) Download Image.

cMapper Use Case
What is the relationship between FGF19 and PDL1 (CD274)?

We have been working on liver cancer genomics. We found a new potential role of FGF19 amplification in hepatocarcinogenesis (Ahn et al., Hepatology 2014). These days, PDL1 (CD274) is a hot issue because PDL1 is the target of immune checkpoint inhibitors, a new promising category of anti-cancer drug.

Tumor cells can express PDL1 to evade immunosurveillance.

We asked a simple question. FGF19 is involved in hepatocarcinogenesis, but can it have anything to do with PDL1?

1. The first thing we did was typing in FGF19 and CD274. Below we present the general landscape of FGF19-CD274 network.

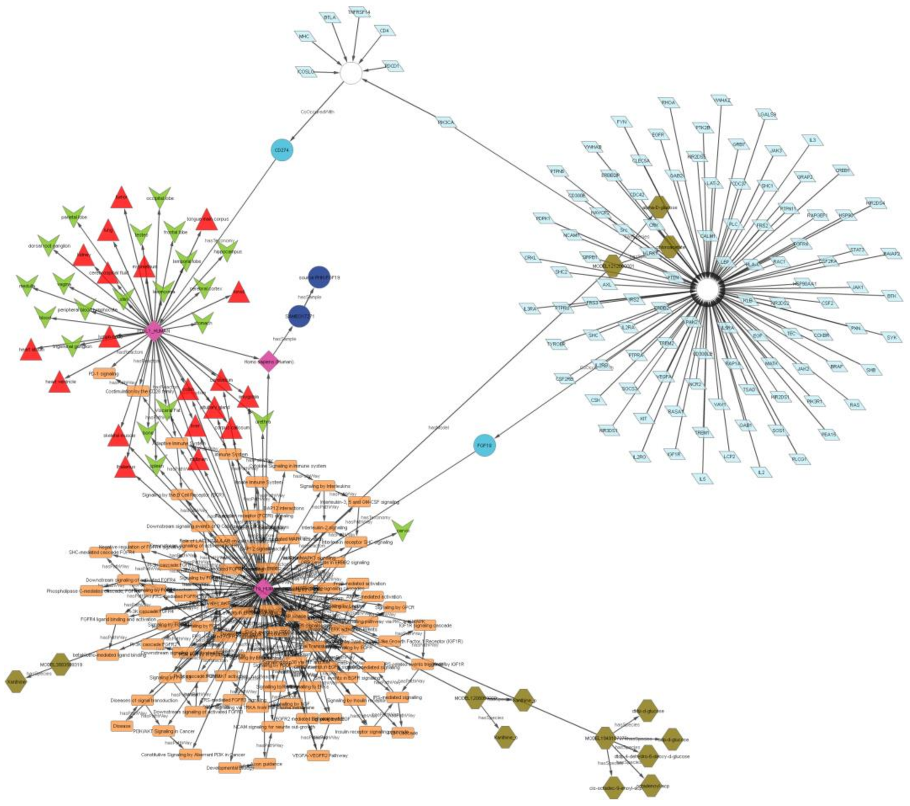


Figure: FGF19 and CD274 Network

2. It was too complex. So we decided to focus on pathways. We only selected REACTOME pathway database.

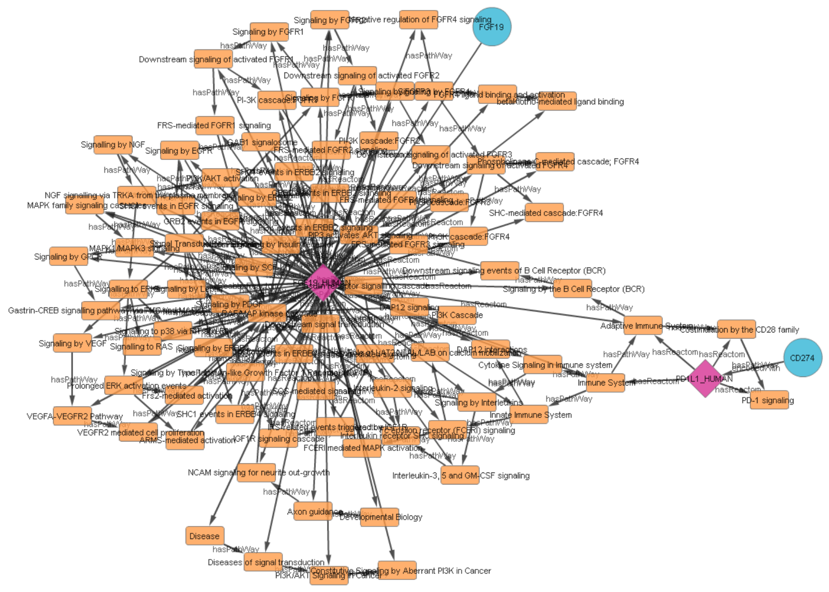

FGF19
CD274
PD1L1_HUMAN
Signaling by FGFR1
Downstream signaling of activated FGFR1
Downstream signaling of activated FGFR2
FRS-mediated FGFR1 signaling
Signaling by NGF
Signaling by EGFR
NGF signalling via TRKA from the plasma membrane
MAPK family signaling cascades
Signaling by GPCR
Gastrin-CREB signalling pathway via PKC and MAPK
Signaling by VEGF
Signaling to RAS
Prolonged ERK activation events
VEGFA-VEGFR2 Pathway
VEGFR2 mediated cell proliferation
ARMS-mediated activation
SHC1 events in ERBB4 signaling
NCAM signaling for neurite out-growth
Axon guidance
Developmental Biology
Disease
Diseases of signal transduction
PI3K/AKT Signaling in Cancer
Constitutive Signaling by Aberrant PI3K in Cancer
Interleukin-3, 5 and GM-CSF signaling
FCERI mediated MAPK activation
Innate Immune System
Immune System
Cytokine Signaling in Immune system
Adaptive Immune System
Costimulation by the CD28 family
PD-1 signaling
Downstream signaling events of B Cell Receptor (BCR)
Signaling by the B Cell Receptor (BCR)
SHC-mediated cascade:FGFR4
Phospholipase C-mediated cascade; FGFR4
betaKlotho-mediated ligand binding
Negative regulation of FGFR4 signaling
hasPathWay
hasReactom

Figure: FGF19 and CD274 Pathways Network

3. Still, it was complex. Since we want to know whether FGF19 and PDL1 have any associated pathways in common, we selected “shared connections”.

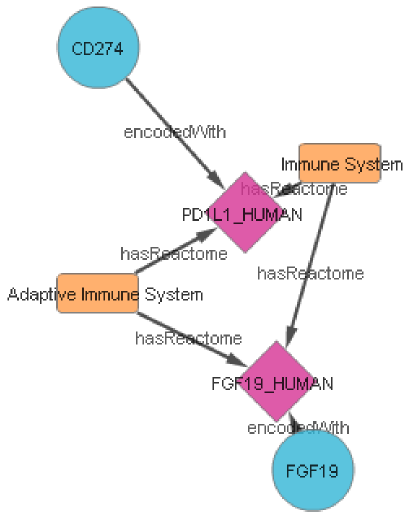


Figure: FGF19 and CD274 Shared Pathways Network

4. Now, we know that the two genes have some shared connections at the pathway level. We wanted to know whether the two genes have any associated genes in common. So, we selected associated genes database and selected “shared connections”.

We found that PIK3CA is related to both FGF19 and PDL1(CD274). Through some more literature search, we have come to a hypothesis that in our liver cancer model system, activation of FGF19-FGFR4 pathway may lead to PDL1 overexpression through PIK3CA pathway. This hypothesis is currently under investigation.

We believe readers can test their molecules of interest very easily. Some searches will provide meaningless results. It is okay, because you will get the same results using EBI-RDF platform and SPARQL queries. But the difference is in that our tool enables you to go through trials and errors in a quick and easy way.

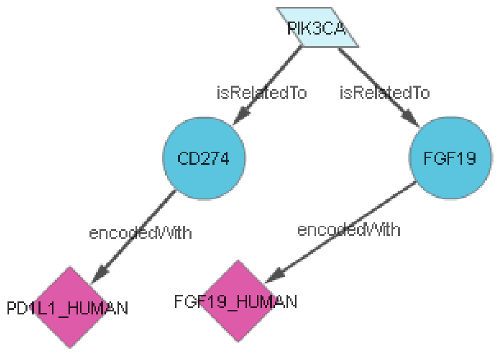


Figure: FGF19 and CD274 Associated Genes Network

References:

Ahn, Sung-Min, et al. "Genomic portrait of resectable hepatocellular carcinomas: implications of RB1 and FGF19 aberrations for patient stratification." Hepatology 60.6 (2014): 1972-1982.

Development Guide

In this section we present overall architecture of our development framework which consists of four major components (1) Data Extraction (2) Data Cleansing or Preprocessing, (3) Relationship construction (4) Web UI.

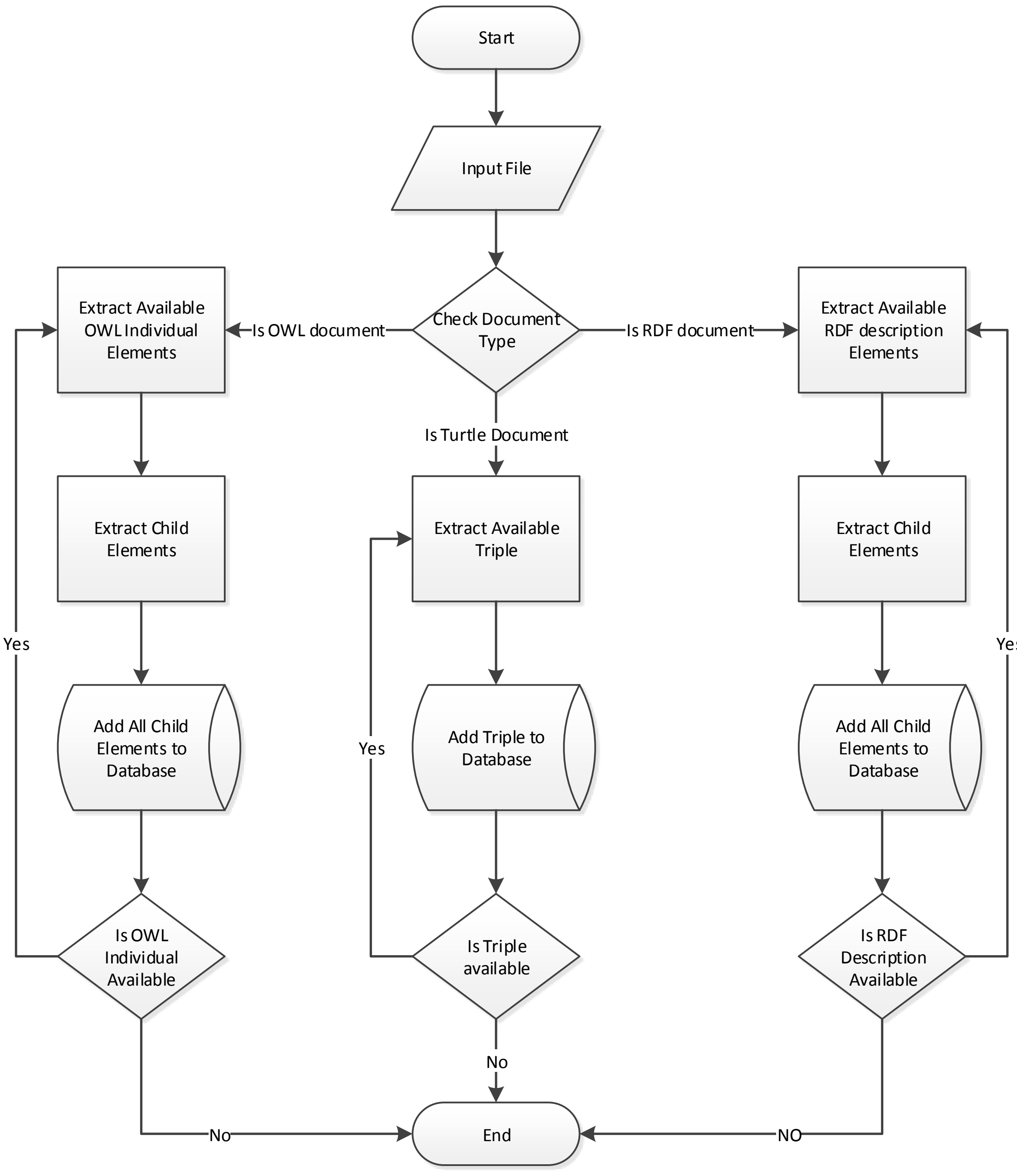


Figure 1a: Flow Chart Representing Data Extraction Process

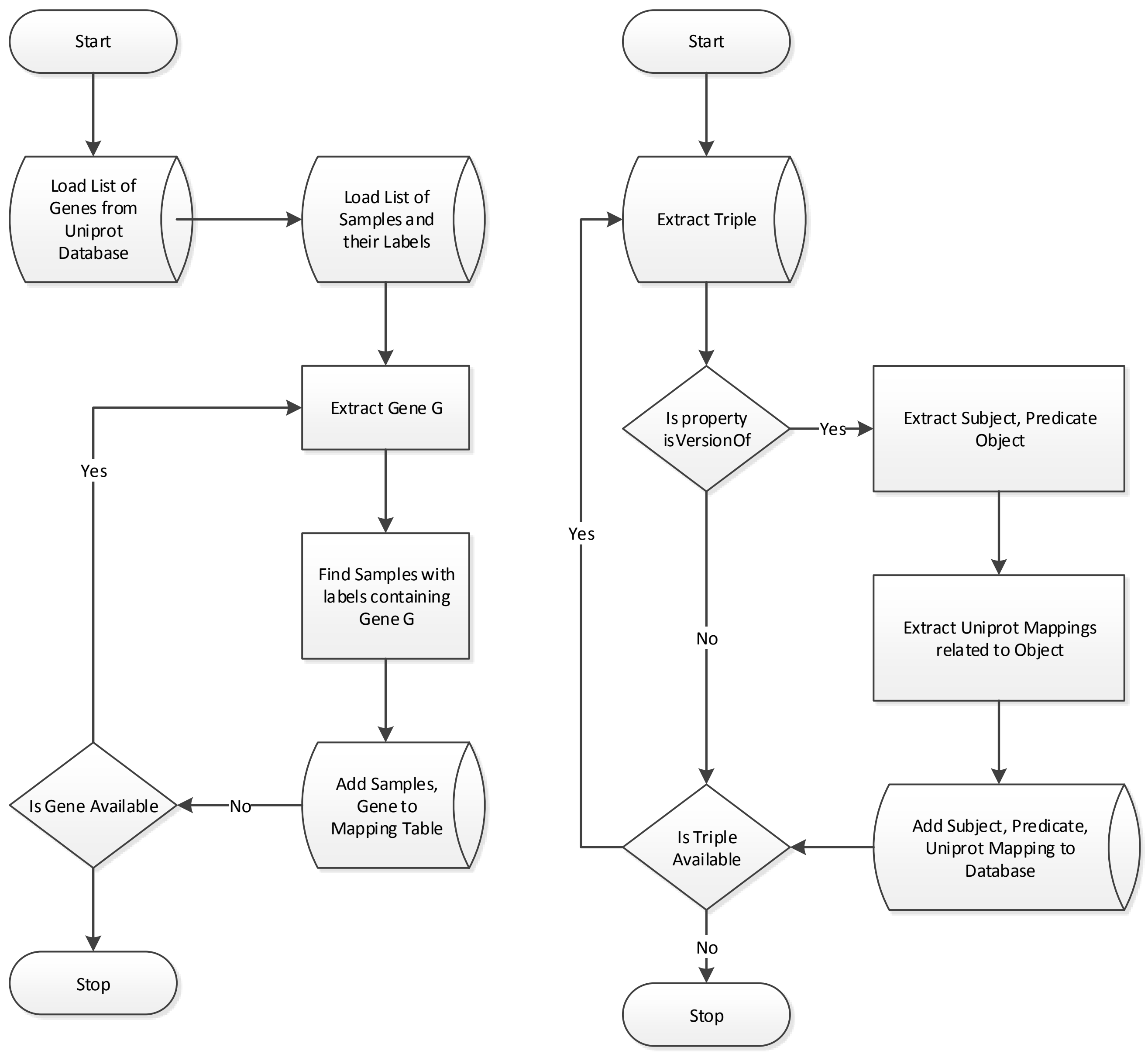

Start
Load List of Genes from Uniprot Database
Load List of Samples and their Labels
Extract Gene G
Yes
Find Samples with labels containing Gene G
Add Samples, Gene to Mapping Table
No
Is Gene Available
Stop
Start
Extract Triple
Is property isVersionOf
Yes
Extract Subject, Predicate Object
Yes
No
Extract Uniprot Mappings related to Object
Add Subject, Predicate, Uniprot Mapping to Database
Is Triple Available
No
Stop

Figure 2b: Flow Chart Representing Data Cleaninsing Process

1. Data Extraction

Figure 1 shows the process of data extraction from different types of RDF documents. The process of data extraction includes (1) extracting data from EBI datasets, and (2) loading them it into the MySQL database. The major challenge that we faced in this module was diversity in data formats. Although EBI claims that it has published data using Semantic Web Technologies i.e. (RDF) whoever they have not standardized their dumps so that they can be used into other applications. RDF dump of UniProt is about 136GB and it is in traditional Graph format so it was really difficult to neither load that RDF data into Database nor process that RDF file because of the hardware limitations. (Notice that our current work is not based cloud technology). On the other hand data about BioSamples is in the N-Triple format.

Figure 3, Figure 4, Figure 5 and Figure 6 presents examples of the data formats in which UniProt, atlas expression, bio samples and bio models data was available. From these figures it can be viewed that data was not in homogeneous format. Similarly the Graphical structures of REACTOME, Atlas and ChEMBL datasets are also not identical so that they can be parsed using simple RDF parser. We wrote six different parsers in Java to parse all six datasets and load them into MySQL database. Since our purpose was to link these six datasets and construct a connectivity graph therefore we only extracted the basic information from the RDF dumps that was sufficient for our tasks. Like we did not extracted biological processes and functions from the UniProt since this information can very easily be obtain by linking the platform with UniProt Database. Similarly we extracted the basic information from Expression atlas in the form of organism parts, assays and experiments details. For ChEMBL we extracted information about Small Molecules and Proteins and Drugs. From REACTOME Dataset we used chemical reactions at all level. Whereas BioSamples and BioMoelds datasets were completely used as they only contain meta-data information. The reason to use subsets was the simplicity at the current stage.

```
ID LCE6A_HUMAN Reviewed; 80 AA.
AC A0A183;
DT 15-JAN-2008, integrated into UniProtKB/Swiss-Prot.
DT 14-NOV-2006, sequence version 1.
DT 24-JUN-2015, entry version 43.
DE RecName: Full=Late cornified envelope protein 6A;
GN Name=LCE6A; Synonyms=C1orf44;
OS Homo sapiens (Human).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
OC Catarrhini; Hominidae; Homo.
OX NCBI_TaxID=9606;
```

```
ID CCNC_XENLA Reviewed; 283 AA.
AC Q4KLA0;
DT 15-JAN-2008, integrated into UniProtKB/Swiss-Prot.
DT 02-AUG-2005, sequence version 1.
DT 27-MAY-2015, entry version 50.
DE RecName: Full=Cyclin-C;
GN Name=ccnc;
OS Xenopus laevis (African clawed frog).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC Amphibia; Batrachia; Anura; Pipoidea; Pipidae; Xenopodinae; Xenopus;
OC Xenopus.
OX NCBI_TaxID=8355;
```

Figure 3 An example of UniProt Text Representation of Protein

```
<http://rdf.ebi.ac.uk/resource/biosamples/sample/SAMN01055052>  rdf:type
 owl:NamedIndividual ;
 biosd-terms:Sample ,
 rdfs:label  E. coli KTE136 Genomic DNA sample Escherichia coli KTE136_A ,
 dcterms:identifier  SAMN01055052 ,
 dcterms:title  E. coli KTE136 Genomic DNA sample Escherichia coli KTE136_A ,
 pav:derivedFrom  <http://rdf.ebi.ac.uk/resource/biosamples/repository-web-record/EBI+Biosamples+Database:SAMN01055052> ;
      <http://rdf.ebi.ac.uk/resource/biosamples/repository-web-record/ebi.ena:SRS346121>,
sio:SIO_000332  <http://rdf.ebi.ac.uk/resource/biosamples/exp-prop-val/GNC-SAMN01055052#0316b3050106570d3e4fb8b9d77c3c3a> ;
     <http://rdf.ebi.ac.uk/resource/biosamples/exp-prop-val/GNC-SAMN01055052#157d2ad03f45a403ba6d8909bd1ef817> ,
biosd-terms:has-bio-characteristic
 <http://rdf.ebi.ac.uk/resource/biosamples/exp-prop-val/GNC-SAMN01055052#c115374bde17ef6c1d997baa2c33d301> ;
 <http://rdf.ebi.ac.uk/resource/biosamples/exp-prop-val/GNC-SAMN01055052#9914abe3168a883712ab6366ac1efae9> ;
 <http://rdf.ebi.ac.uk/resource/biosamples/exp-prop-val/GNC-SAMN01055052#b8e2cfc7f5777e8628008851bb0aafac> ;
 <http://rdf.ebi.ac.uk/resource/biosamples/exp-prop-val/GNC-SAMN01055052#bee811c79426f216d654f91b5830f9ed> ;
 <http://rdf.ebi.ac.uk/resource/biosamples/exp-prop-val/GEN-SRA053203#9914abe3168a883712ab6366ac1efae9> ;
 <http://rdf.ebi.ac.uk/resource/biosamples/exp-prop-val/GEN-SRA053203#b8e2cfc7f5777e8628008851bb0aafac> .
```

Figure 4 An example of BioSamples XML objects

```
<owl:NamedIndividual rdf:about="http://purl.uniprot.org/uniprot/A0A183">
     <rdf:type rdf:resource="http://rdf.ebi.ac.uk/terms/atlas/UniprotDatabaseReference"/>
     <rdfs:label rdf:datatype="http://www.w3.org/2001/XMLSchema#string">A0A183</rdfs:label>
     <terms:identifier rdf:datatype="http://www.w3.org/2001/XMLSchema#string">A0A183</terms:identifier>
  </owl:NamedIndividual>
<owl:NamedIndividual rdf:about="http://rdf.ebi.ac.uk/resource/atlas/A-AFFY-11:64786_at">
     <atlas:dbXref rdf:resource="http://identifiers.org/ensembl/ENSG00000235942"/>
     <atlas:dbXref rdf:resource="http://identifiers.org/ncbigene/448835"/>
     <atlas:dbXref rdf:resource="http://purl.uniprot.org/uniprot/A0A183"/>
  </owl:NamedIndividual>
  <owl:NamedIndividual rdf:about="http://rdf.ebi.ac.uk/resource/atlas/A-MEXP-2246:2359420">
     <atlas:dbXref rdf:resource="http://identifiers.org/ensembl/ENSG00000235942"/>
     <atlas:dbXref rdf:resource="http://identifiers.org/ncbigene/448835"/>
     <atlas:dbXref rdf:resource="http://purl.uniprot.org/uniprot/A0A183"/>
  </owl:NamedIndividual>
```

Figure 5 An example of Atlas XML objects

```
<rdf:Description rdf:about="http://purl.uniprot.org/uniprot/Q4KLA0">
   <owl:sameAs rdf:resource="http://identifiers.org/uniprot/Q4KLA0"/>
 </rdf:Description>
 <rdf:Description rdf:about="http://identifiers.org/biomodels.db/BIOMD0000000003#_230475">
   <sbmlRdf:inCompartment rdf:resource="http://identifiers.org/biomodels.db/BIOMD0000000003#_230461"/>
   <sbmlRdf:name>Cyclin</sbmlRdf:name>
   <sbmlRdf:initialConcentration rdf:datatype=
    "http://www.w3.org/2001/XMLSchema#double">0.01</sbmlRdf:initialConcentration>
   <bqbiol:isVersionOf rdf:resource="http://identifiers.org/interpro/IPR006670"/>
   <sbmlRdf:constant rdf:datatype=
    "http://www.w3.org/2001/XMLSchema#boolean">false</sbmlRdf:constant>
   <sbmlRdf:initialAmount rdf:datatype=
    "http://www.w3.org/2001/XMLSchema#double">NaN</sbmlRdf:initialAmount>
   <sbmlRdf:boundaryCondition rdf:datatype=
    "http://www.w3.org/2001/XMLSchema#boolean">false</sbmlRdf:boundaryCondition>
   <bqbiol:isVersionOf rdf:resource="http://purl.uniprot.org/uniprot/Q4KLA0"/>
   <rdf:type rdf:resource="http://identifiers.org/biomodels.vocabulary#Species"/>
   <bqbiol:is rdf:resource="http://identifiers.org/biomodels.sbo/SBO:0000252"/>
   <sbmlRdf:hasOnlySubstanceUnits rdf:datatype=
    "http://www.w3.org/2001/XMLSchema#boolean">false</sbmlRdf:hasOnlySubstanceUnits>
   <sbmlRdf:substanceUnits rdf:datatype=
    "http://www.w3.org/2001/XMLSchema#string">substance</sbmlRdf:substanceUnits>
   </rdf:Description>
```

Figure 6 An example of BioModel XML objects

2. Data Cleansing

In most of the databases / triple store direct connections exists with UniProt however this is not the case for each and every dataset. Consider the example of BioModeles database where we have few UniProt identifications whereas links with other databases like Ensamble etc. exits. Since our framework is constructed by considering UniProt as the baseline therefore we had to convert those mapping into UniProt mappings because we took UniProt and Gene Names as the stranded for data normalization process. This process was undertaken by Data Normalization module of the framework. Luckily UniProt provides the mapping to proteins entities with other databases that was used for normalization of BioModeles. In the previous section we have explained that how we found the bridged properties between databases. In the process of data normalization we first extracted those bridged properties that bridge BioModeles with UniProt mainly. In the next step we check the diversity in the ranges of those properties which were identified as bridged. For each of object value of those properties we mapped them with available UniProt Values. After this exercise all non-UniProt identifier were replaced with UniProt identifiers. The same exercise was performed with the BioSample Database the difference between normalization of BioModeles database and BioSample database was that BioSample was normalized based on Genes Names instead of UniProt Identifiers. There was no mapping available for

Gene Names therefore we have to map each sample-gene relationship manually. The process of mapping gene-sample was computationally expensive but was a onetime effort as for each gene we have to search for relevant samples and add them to mapping table.

3. Identifying the bridge properties

As explained Bridge properties are those which has subject in one dataset and object in other dataset.

Let $T_1 = \{S_1, P_1, O_1\}$ and $T_2 = \{S_2, P_2, O_3\}$ be two different triple stores, a property $p_{\{11\}} \in P_1$ is called bridged if and if only if $Domain(p_{\{11\}}) \subset S_1 \wedge Range(p_{\{11\}}) \subset O_2$ or $Domain(p_{\{11\}}) \subset S_2 \wedge Range(p_{\{11\}}) \subset O_1$ or vice versa.

To identify the bridge properties we first loaded each triple store into MySQL database as explained in {Data Extraction} section. We then extracted all properties using {rdf:type} as for each property {?p} there exists a triple {?p rdf:type owl:Property} from each triple store and insert them into global properties table along with triple store identifier. This task can be accomplished by comparing the set of domains and ranges of each property with each other properties however this operation is computationally expensive and not possible. Consider two similar properties p_1 with domain D_1 and range R_1 and p_2 with domain D_2 and range R_2 and we have to find whether p_1 is similar to p_2 and vice versa. The time complexity will be $min(|D_1|, |D_2|) \times minn(|R_1|, |R_2|)$. Therefore instead of finding all bridge properties we first manually selected potential bridged properties who can play key role in interlinking two databases. For example for integrating atlas database with UniProt we searched for those properties that has link with either UniProt ID or Gene Name. Similar kind of exercise was done for ChEMBL and REACTOME databases. For BioSamples we extracted properties that contain links with Gene Name and Expression Atlas.

Once we identified the bridge properties, standardized them, the next step was the standardization the names of their domains and ranges since they varies from database to database.

4. Network Construction

Since these all triple stores were not constructed by single community therefore there dumps are available with an identical Ontology. To add these triple stores in our biomedical knowledgeable we have to normalize their IRIs. In the first step we remove all the prefixes from the properties by replacing with their real IRIs. The next step was for Atlas, Bio Samples and Bio Models in which we add mapping triples for genes and proteins as no triple describing the relationships of samples, models and expressions with genes were present in the original triple stores. To do so, we identified the potential properties whose object may have the names of genes and proteins. As these properties does not lead to direct required objects, i.e. samples or models so for each identified property we manually traced the hierarchy which leads to either sample model or experiment. We then constructed the separate queries for each identified properties to construct the links between the objects of identified properties (i.e. genes or proteins) and expressions, models and samples. By the end of this exerciser we had information that which expression, sample and model are linked with which genes and proteins.

5. Web Portal

Web portal was the last step of framework development which provides users an interface to search for any particular gene or small molecule to get its links in other databases. As no such prototype is available already that can be borrowed so we developed in house java based portal to provide this functionality to the users. When a user input a gene or small molecule and select particular databases, as the output he gets a graph with the data points as nodes and links among those nodes as edges. Nodes belonging to different databases are colored differently to ensure readability. We used Cytoscape (a well-known software for graph construction)'s web API to constitute the graphs.

Figure 7 and Figure 8 show the procedural pipelines that web portal performs after receiving a gene or small molecule as query. For a small molecule in the first step list of those proteins and genes which are regulated by given drug are extracted. In the second step list of proteins are given as input to expression atlas, CheMBL, REACTOME and BioModels and genes to BioSamples to extract all possible entities associated with gene(s) and their proteins. After extraction of entities from all databases they are fused to create one comprehensive graph. The resulted graph is then transferred into GraphML and returns to user agent (Web Browser) which stores the GraphML or creates a visualized graph from it according the users' requirements.

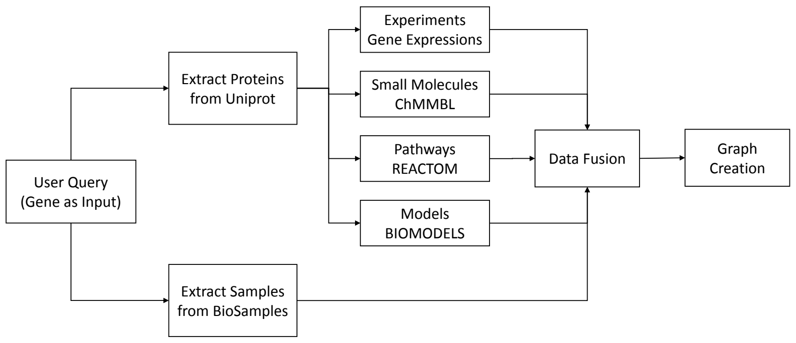


Figure 7 Procedural pipeline of graph creation for a User Query (Gene)

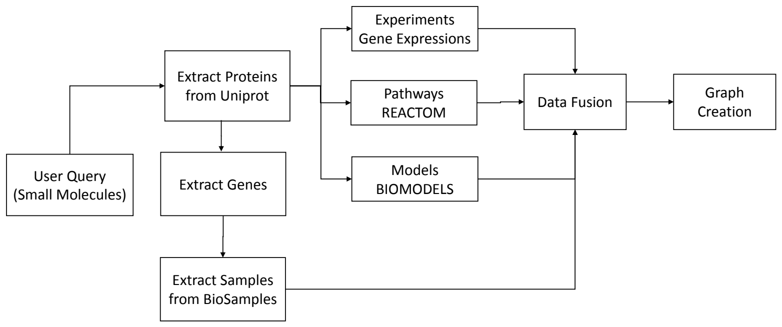


Figure 8 Procedural pipeline of graph creation for a User Query (Drug)