HOUSTON Methodist LEADING MEDICINE

DrugComboRanker

Version 1.0.0

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Revision History

Version	Date	Description	Created By	Reviewed By
1.0	6/6/2018	User Guide	Xiaohui Yu/ Lei Huang	Stephen Wong

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Contents

Introduction

Motivation:

Currently there are no curative anticancer drugs, and drug resistance is often acquired after drug treatment. One of the reasons is that cancers are complex diseases, regulated by multiple signaling pathways and cross talks among the pathways. It is expected that drug combinations can reduce drug resistance and improve patients' outcomes. In clinical practice, the ideal and feasible drug combinations are combinations of existing Food and Drug Administration-approved drugs or bioactive compounds that are already used on patients or have entered clinical trials and passed safety tests. These drug combinations could directly be used on patients with less concern of toxic effects. However, there is so far no effective computational approach to search effective drug combinations from the enormous number of possibilities.

Results:

In this study, we propose a novel systematic computational tool DrugComboRanker to prioritize synergistic drug combinations and uncover their mechanisms of action. We first build a drug functional network based on their genomic profiles, and partition the network into numerous drug network communities by using a Bayesian non-negative matrix factorization approach. As drugs within overlapping community share common mechanisms of action, we next uncover potential targets of drugs by applying a recommendation system on drug communities. We meanwhile build disease-specific signaling networks based on patients' genomic profiles and interactome data. We then identify drug combinations by searching drugs whose targets are enriched in the complementary signaling modules of the disease signaling network. The novel method was evaluated on lung adenocarcinoma and endocrine receptor positive breast cancer, and compared with other drug combination approaches. These case studies discovered a set of effective drug combinations top ranked in our prediction list, and mapped the drug targets on the disease signaling network to highlight the mechanisms of action of the drug combinations.

If you have any questions, please contact Lei Huang (lhuang@houstonmethodist.org), Xiaohui Yu(xyu2@houstonmethodist.org) or Stephen Wong (STWong@houstonmethodist.org)

Please cite the following paper when you use DrugComboRanker.

DrugComboRanker: drug combination discovery based on target network analysis. Lei Huang, Fuhai Li, Jianting Sheng, Xiaofeng Xia, Jinwen Ma, Ming Zhan and Stephen T.C. Wong, 2014. 30:i228–i236

System requirements

The minimum of system requirements for DrugComboRanker

Hardware:

Processor 2GHz

Memory 4Gb

Graphics Card On board Video

Monitor XGA (1024X768)

Software:

Java SE Runtime Environment 7 or higher

Python 2.7.x

R language version 3.2.0 or higher

Getting Started

Install and run DrugComboRanker on Windows OS

- **Install Java JRE**
  DrugComboRanker is a Java-based application. If Java is not installed on your computer, please download and install Java SE 7 or higher. The JRE package is available from:

  http://www.oracle.com/technetwork/java/javase/downloads/jre7-downloads-1880261.html

- **Install R language and dependent packages**
  Download R language (V3.2-0 or higher)/R studio for Windows from https://cran.r-project.org/bin/windows/base/ and http://cran.rstudio.com/Install R.

  DrugComboRanker uses igraph R package. To install this package, open RGui and run the command below.

```
>install.packages("igraph")
```

- **Add the R path to the system environment**
  For example, the current R installed path is C:\Program Files\R\R-3.4.1\bin.

  Go to **System Properties**->**Environment Variables** to add the R path to the Path variable. Eg. Figure 1.

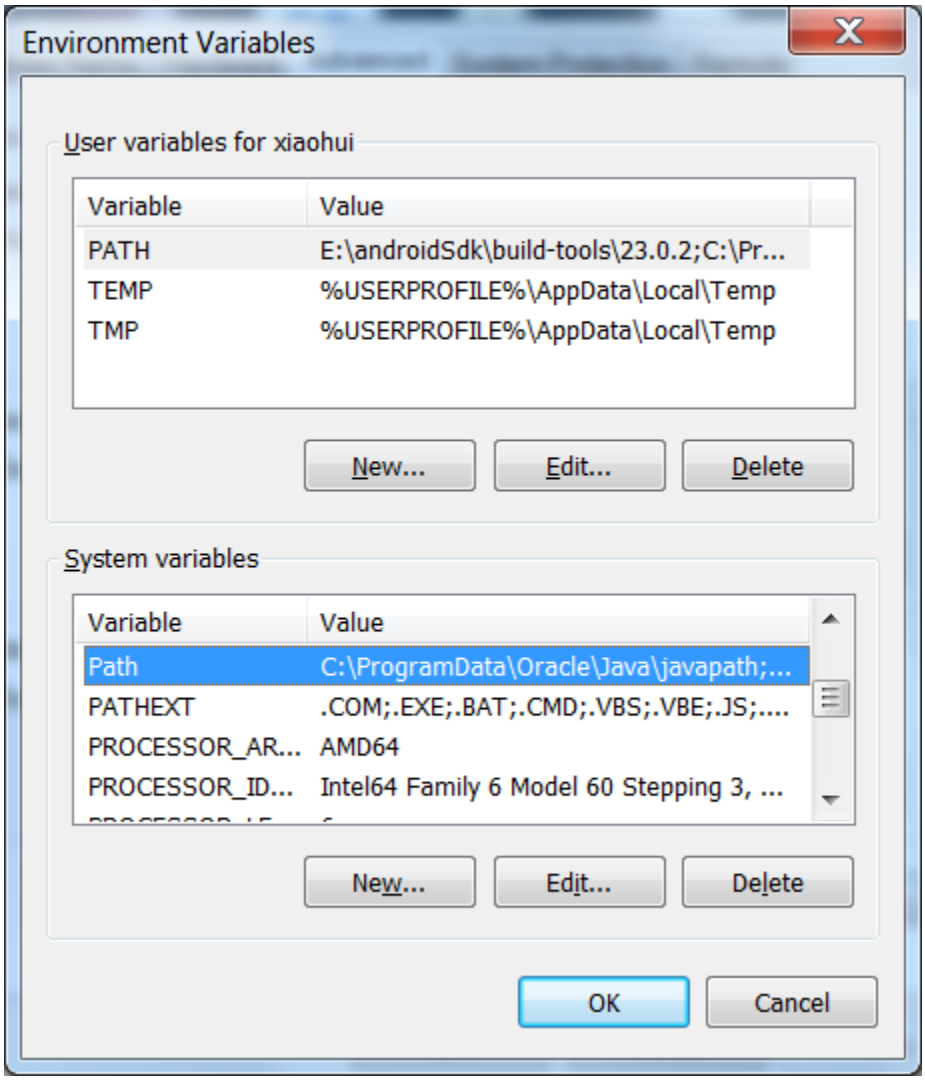

Figure 1

- **Run DrugComboRanker**
  Decompress DrugComboRanker.zip

Double click run_drug_combination.bat in the DrugComboRanker folder. The DrugComboRanker will be opened as the Figure 2.

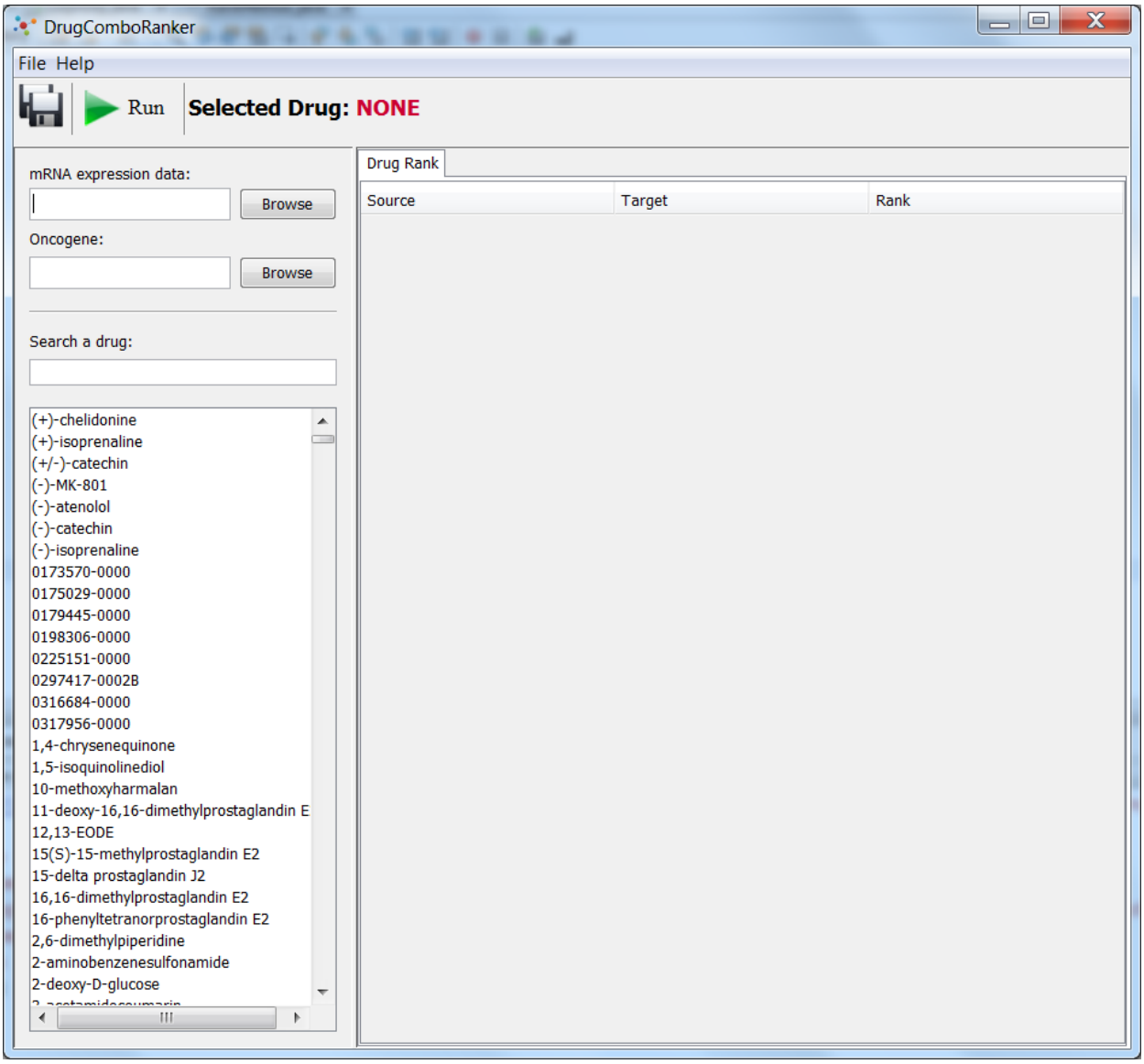

Figure 2

There are two input files that you need to input. One is mRNA different gene data and the cancer gene data. Users have to generate their own High Inter connected genes network using these two files.

1. Go to folder **network_high_interconnect** and run the script below.

```
win_run.bat differ_expr_gene_gse10072.txt lung_cancer_gene_gse10072.txt
```

This script will take about 50 minutes with the sample data. It will take a longer time that depends on the gene numbers of these input files.

The generated file name is that below:

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High_inter_connected_gse_biogrid.txt

Copy this file to the input_data folder.

2. User can run **run_drug_combination.bat** to start using DrugComboRanker.

Note that:

User needs to re-generate the High Inter Connected Genes with the step 1 if users change these two input files.

3. Select the mRNA expression genes, oncogene and a drug, then click Run button.

The DrugComboRanker will calculate the ranks. The ranks will be listed in the table on the right. Eg. Figure 3.

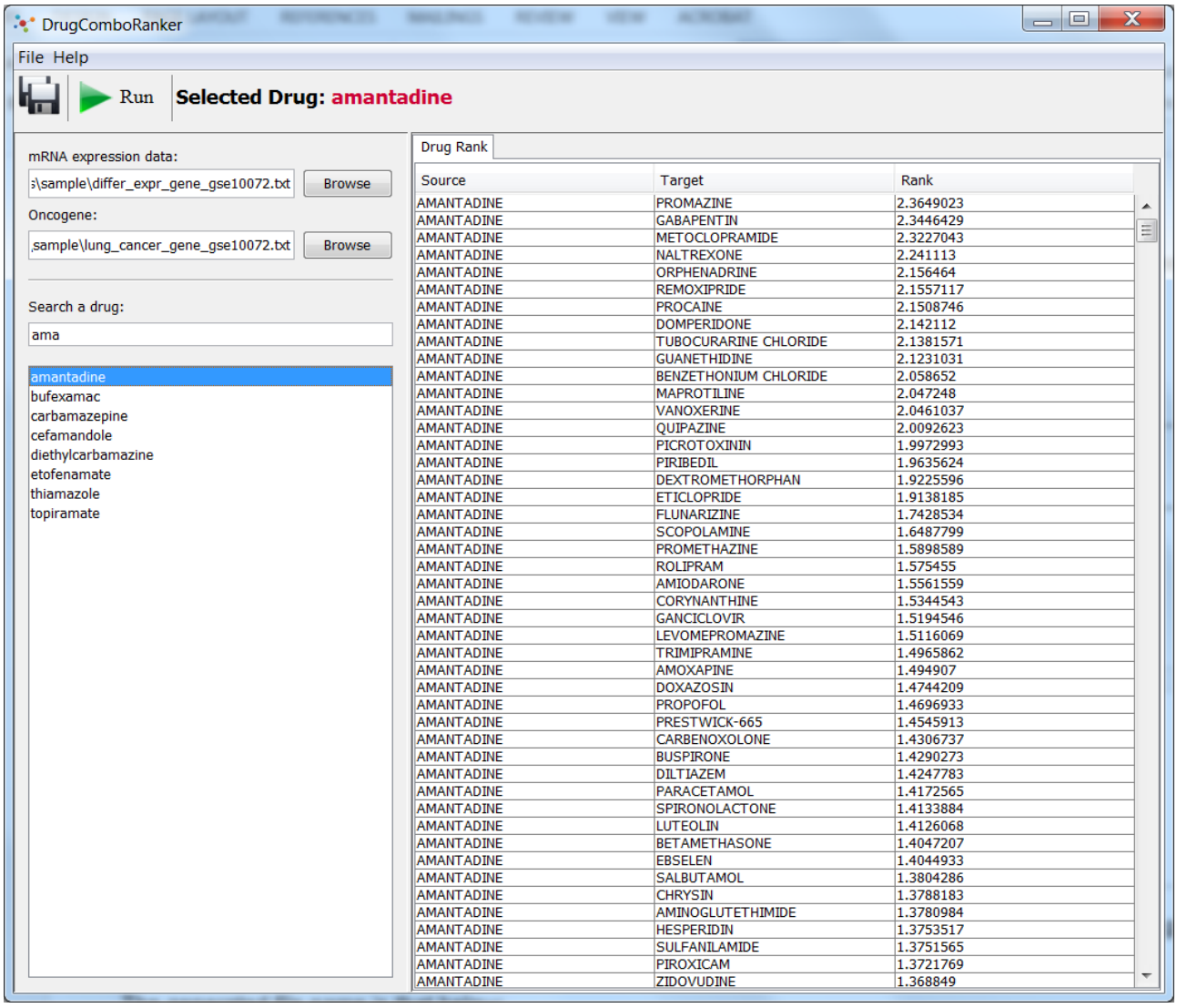


Figure 3

4. Click a row of the table, DrugComboRanker will display all related pathways. Eg. Figure 4.

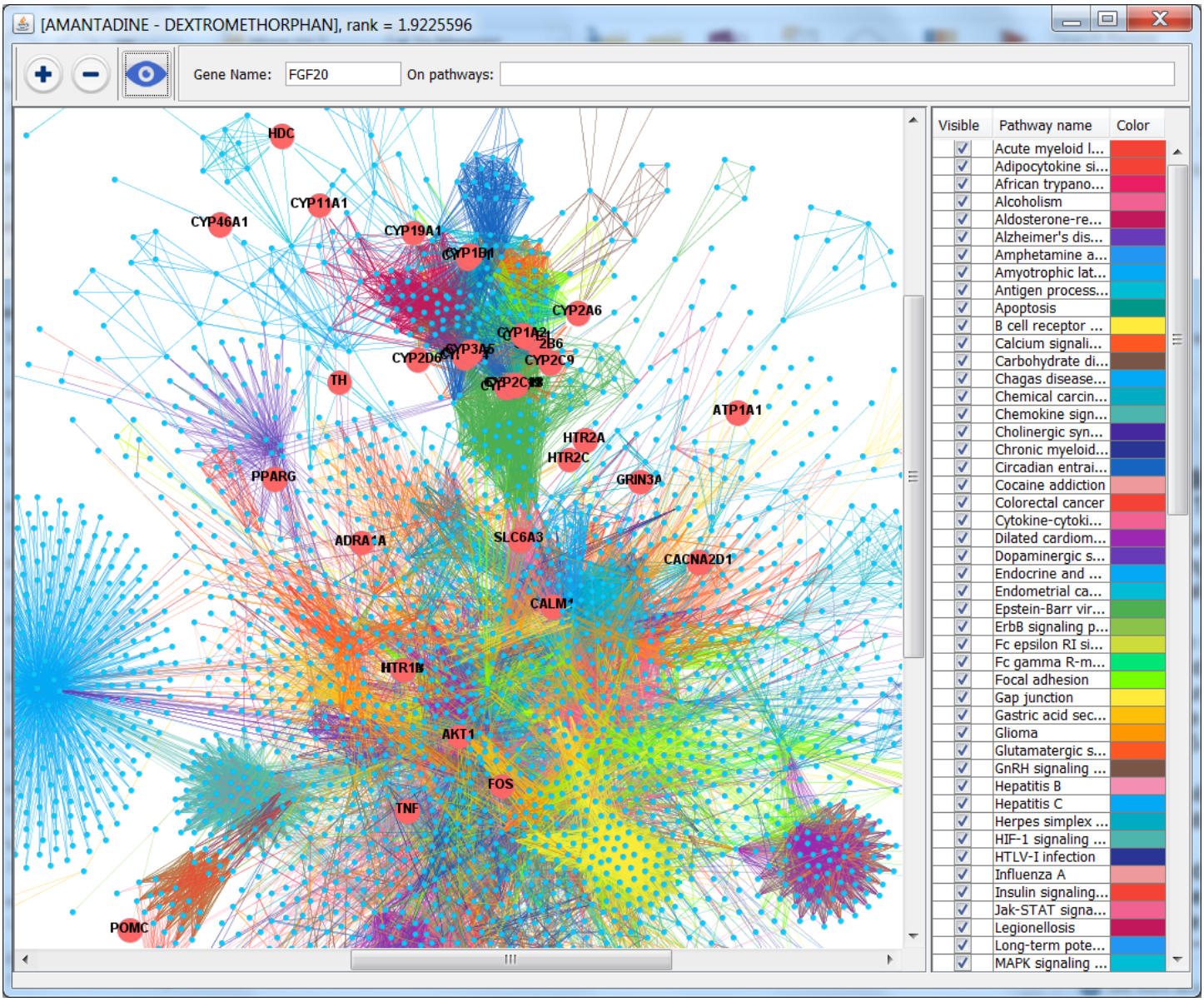


Figure 4

Install and run DrugComboRanker running environment on Ubuntu

- **Install the dependent libraries**
  Install Java runtime environment

```
sudo apt-get install default-jre
```

Install the R runtime environment

```
sudo apt-get install r-base-core
```

- **Install Python 2.7.x package**

```
sudo apt update

sudo apt upgrade

sudo apt install python2.7 python-pip

sudo apt install python3-pip
```

- **Install R package**

  Run R command in the terminal and install the R package “igraph”.

```
xxxhuis:user$ R

>install.packages("igraph")
```

- **Run DrugComboRanker**

  Decompress DrugComboRanker.zip

```
unzip  DrugComboRanker.zip
```

In the DrugComboRanker folder, run the following command to open DrugComboRanker as Figure 4

```
Java –jar DrugCombination.jar
```

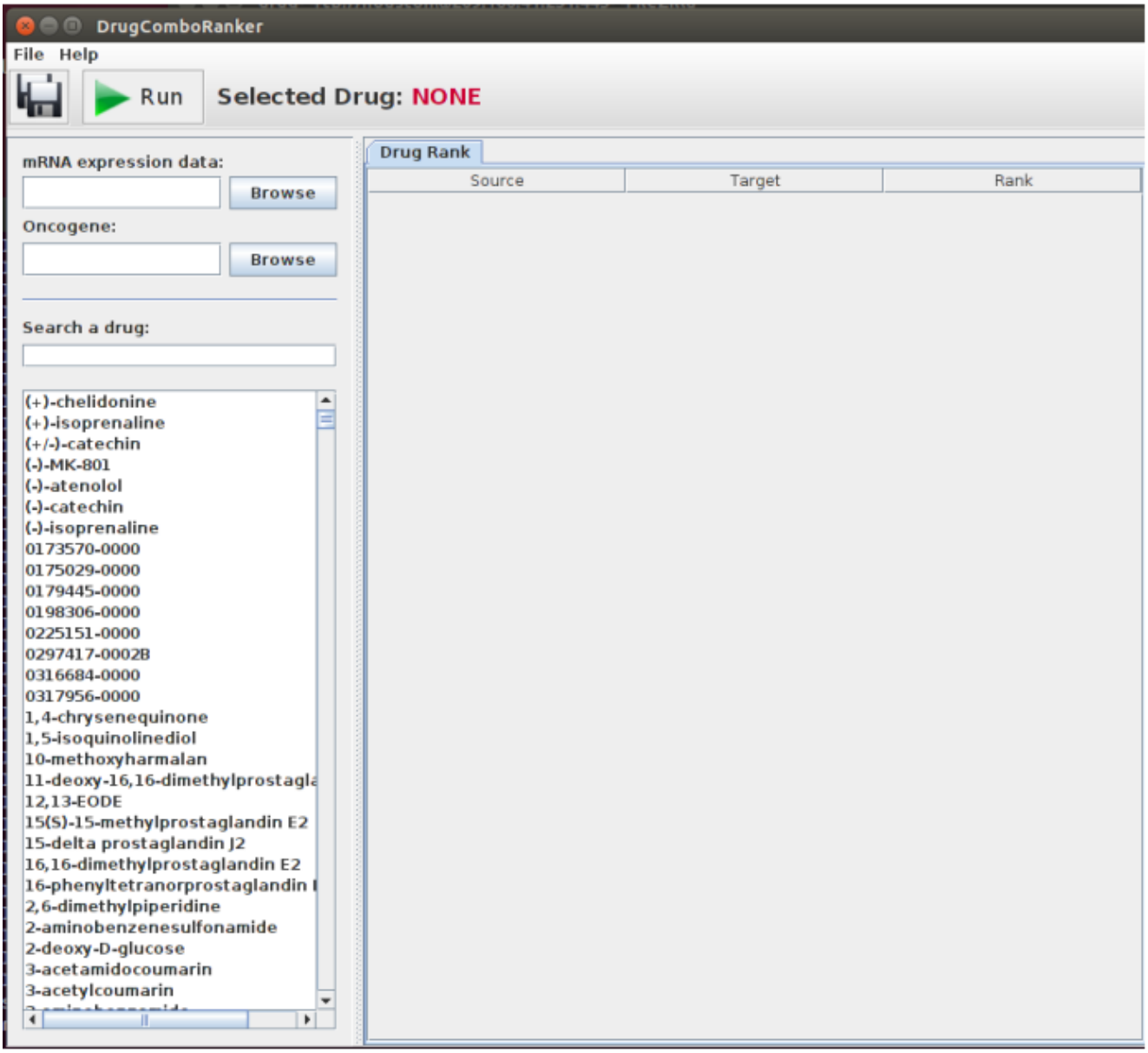


Figure 5

There are two input files that you need to input. One is mRNA different gene data and the cancer gene data.

Users have to generate their own High Inter connected genes network using these two files.

1. Go to folder **network_high_interconnect** and run the script below.

```
sudo chmod +x linux_run.sh

./linux_run.sh differ_expr_gene_gse10072.txt lung_cancer_gene_gse10072.txt
```

This script will take about 50 minutes with the sample data. It will take a longer time that depends on the gene numbers of these input files.

The generated file name is that below:

```
High_inter_connected_gse_biogrid.txt
```

Copy this file to the input_data folder.

2. User can run the command below to start using DrugComboRanker.

```
Java –jar DrugCombination.jar
```

Note that:

User needs to generate the High Inter Connected Genes with the step 1 if users change these two input files.

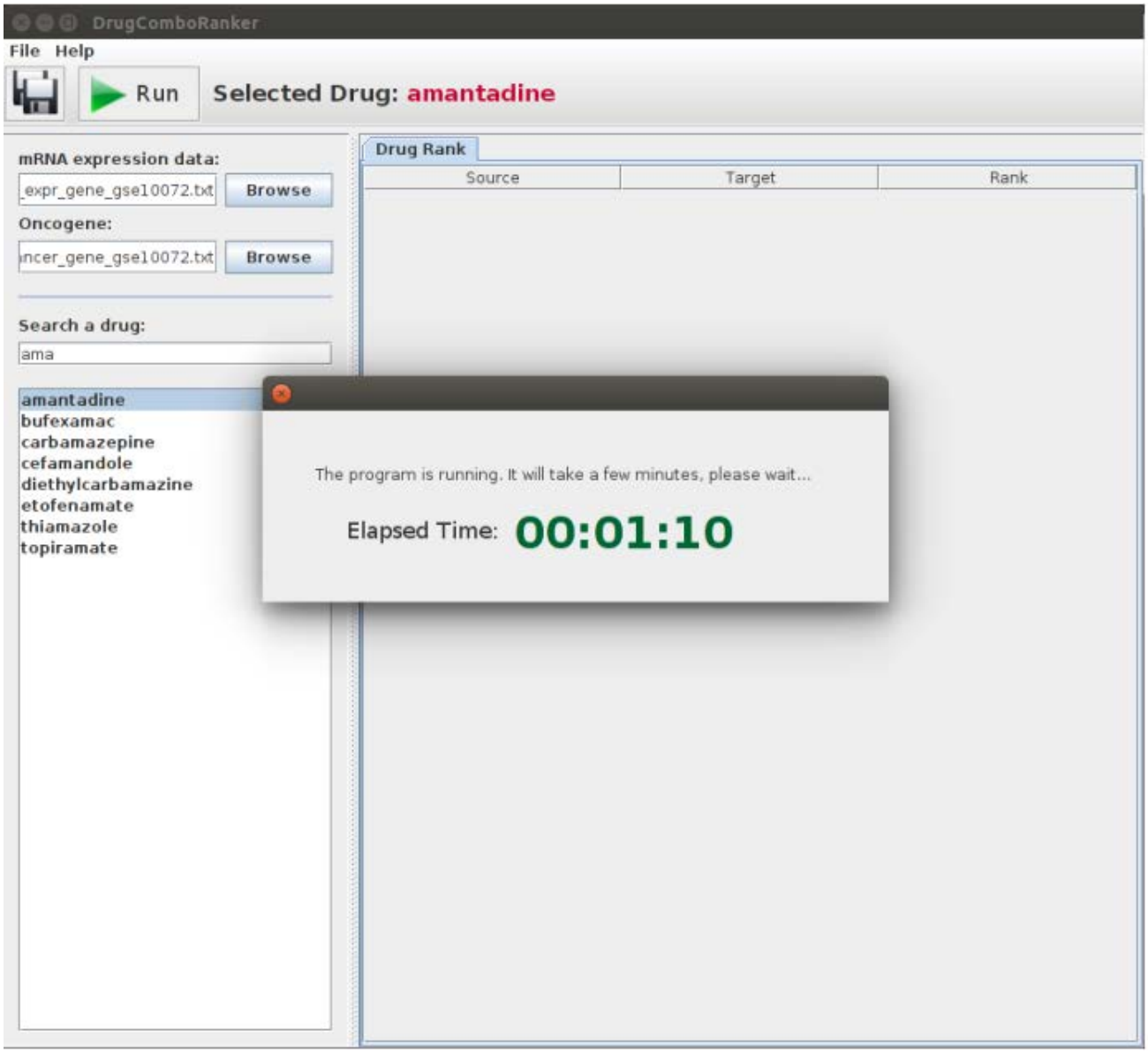
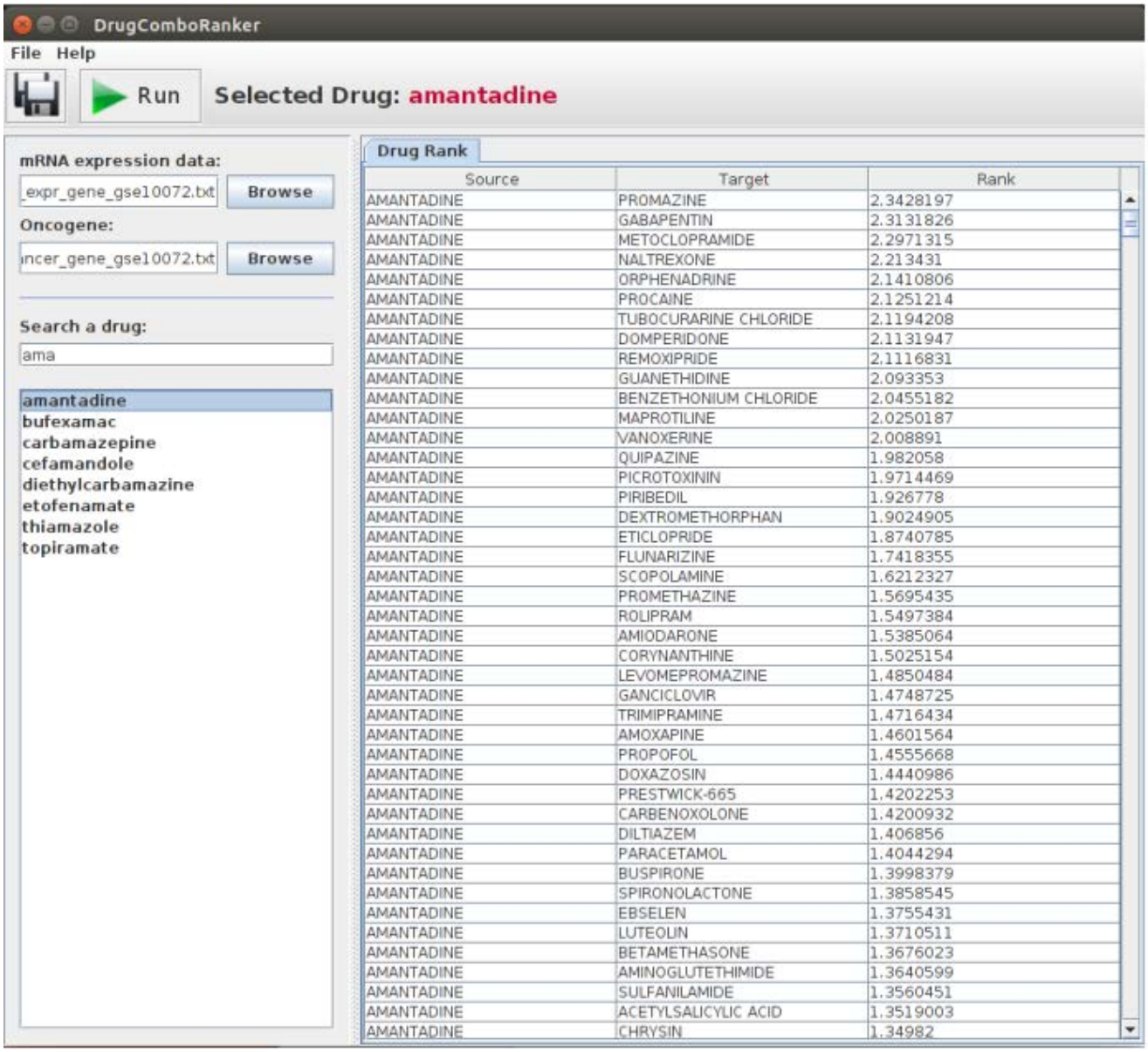


Figure 6

3. Select the mRNA expression genes, oncogene and a drug, then click Run button.

The DrugComboRanker will calculate the ranks. The ranks will be listed in the table on the right. Eg. Figure 7.



Source	Target	Rank
AMANTADINE	PROMAZINE	2.3428197
AMANTADINE	GABAPENTIN	2.3131826
AMANTADINE	METOCLOPRAMIDE	2.2971315
AMANTADINE	NALTREXONE	2.213431
AMANTADINE	ORPHENADRINE	2.1410806
AMANTADINE	PROCAINE	2.1251214
AMANTADINE	TUBOCURARINE CHLORIDE	2.1194208
AMANTADINE	DOMPERIDONE	2.1131947
AMANTADINE	REMOXIPRIDE	2.1116831
AMANTADINE	GUANETHIDINE	2.093353
AMANTADINE	BENZETHONIUM CHLORIDE	2.0455182
AMANTADINE	MAPROTILINE	2.0250187
AMANTADINE	VANOXERINE	2.008891
AMANTADINE	QUIPAZINE	1.982058
AMANTADINE	PICROTOXININ	1.9714469
AMANTADINE	PIRIBEDIL	1.926778
AMANTADINE	DEXTROMETHORPHAN	1.9024905
AMANTADINE	ETICLOPRIDE	1.8740785
AMANTADINE	FLUNARIZINE	1.7418355
AMANTADINE	SCOPOLAMINE	1.6212327
AMANTADINE	PROMETHAZINE	1.5695435
AMANTADINE	ROLIPRAM	1.5497384
AMANTADINE	AMIODARONE	1.5385064
AMANTADINE	CORYNANTHINE	1.5025154
AMANTADINE	LEVOMEPROMAZINE	1.4850484
AMANTADINE	GANCICLOVIR	1.4748725
AMANTADINE	TRIMIPRAMINE	1.4716434
AMANTADINE	AMOXAPINE	1.4601564
AMANTADINE	PROPOFOL	1.4555668
AMANTADINE	DOXAZOSIN	1.4440986
AMANTADINE	PRESTWICK-665	1.4202253
AMANTADINE	CARBENOXOLONE	1.4200932
AMANTADINE	DILTIAZEM	1.406856
AMANTADINE	PARACETAMOL	1.4044294
AMANTADINE	BUSPIRONE	1.3998379
AMANTADINE	SPIRONOLACTONE	1.3858545
AMANTADINE	EBSELEN	1.3755431
AMANTADINE	LUTEOLIN	1.3710511
AMANTADINE	BETAMETHASONE	1.3676023
AMANTADINE	AMINOGLUTETHIMIDE	1.3640599
AMANTADINE	SULFANILAMIDE	1.3560451
AMANTADINE	ACETYLSALICYLIC ACID	1.3519003
AMANTADINE	CHRYSIN	1.34982

Figure 7

4. Click a row of the table, DrugComboRanker will display all related pathways. Eg. Figure 8.

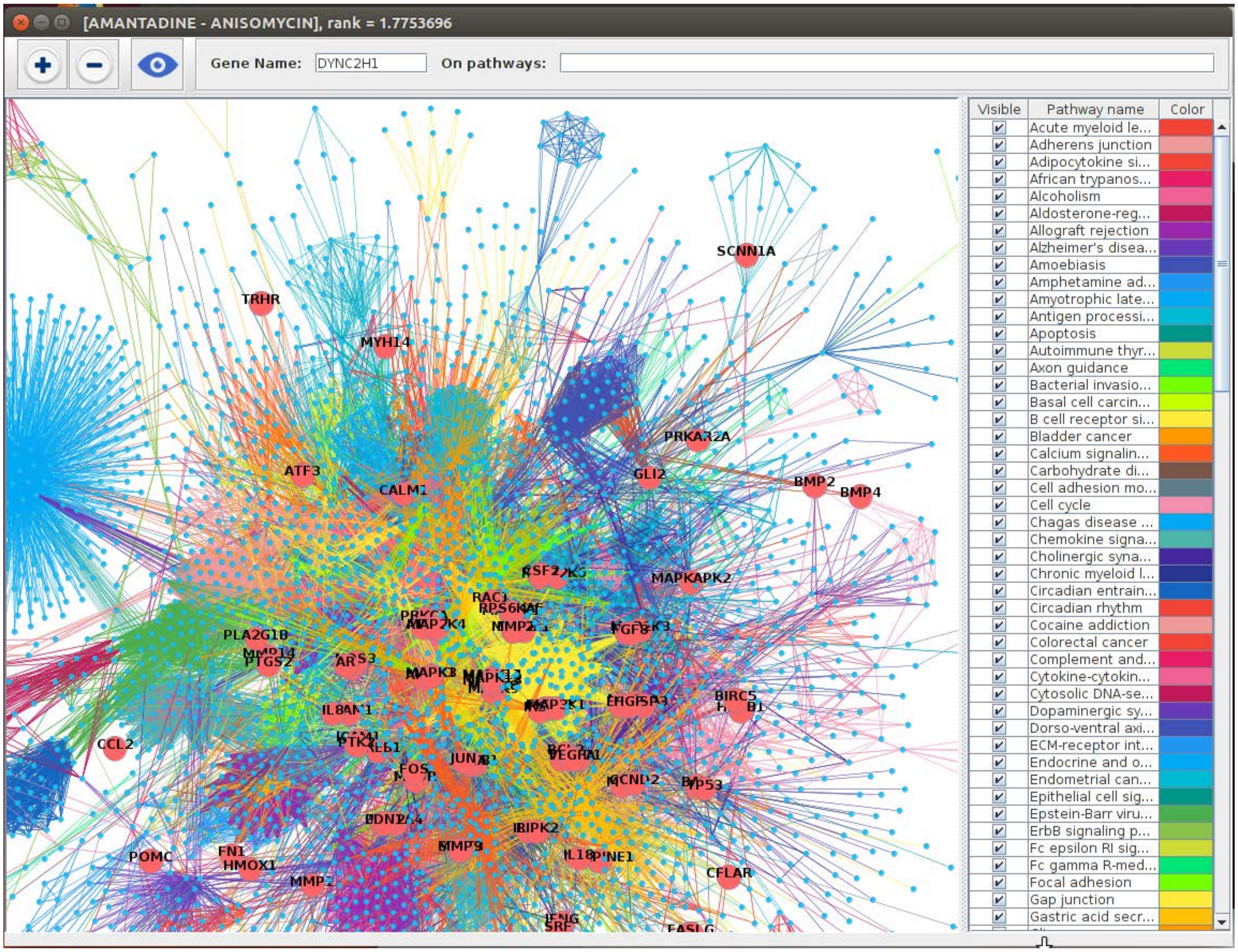

[AMANTADINE - ANISOMYCIN], rank = 1.7753696
Gene Name:
DYNC2H1
On pathways:
Visible
Pathway name
Color
Acute myeloid le...
Adherens junction
Adipocytokine si...
African trypanos...
Alcoholism
Aldosterone-reg...
Allograft rejection
Alzheimer's disea...
Amoebiasis
Amphetamine ad...
Amyotrophic late...
Antigen processi...
Apoptosis
Autoimmune thyr...
Axon guidance
Bacterial invasio...
Basal cell carcin...
B cell receptor si...
Bladder cancer
Calcium signalin...
Carbohydrate di...
Cell adhesion mo...
Cell cycle
Chagas disease ...
Chemokine signa...
Cholinergic syna...
Chronic myeloid l...
Circadian entrain...
Circadian rhythm
Cocaine addiction
Colorectal cancer
Complement and...
Cytokine-cytokin...
Cytosolic DNA-se...
Dopaminergic sy...
Dorso-ventral axi...
ECM-receptor int...
Endocrine and o...
Endometrial can...
Epithelial cell sig...
Epstein-Barr viru...
ErbB signaling p...
Fc epsilon RI sig...
Fc gamma R-med...
Focal adhesion
Gap junction
Gastric acid secr...
SCNN1A
TRHR
MYH14
PRKAR2A
ATF3
CALM1
GLI2
BMP2
BMP4
MAPKAPK2
PLA2G1B
PTGS2
CCL2
BIRC5
FOS
MMP3
POMC
FN1
HMOX1
CFLAR
RIPK2

Figure 8