DrugComboExplorer

Version 1.0.0

Revision History

Version	Date	Description	Created By	Reviewed By
1.0	4/6/2019	User Guide	Xiaohui Yu	Stephen Wong

Contents

Introduction

Motivation:

Drug combinations that simultaneously suppress multiple cancer driver signaling pathways increase therapeutic options and may reduce drug resistance. We have developed a computational systems biology tool, DrugComboExplorer, to identify driver signaling pathways and predict synergistic drug combinations by integrating the knowledge embedded in vast amounts of available pharmacogenomics and omics data.

Results:

This tool generates driver signaling networks by processing DNA sequencing, gene copy number, DNA methylation, and RNA-seq data from individual cancer patients using an integrated pipeline of algorithms, including bootstrap aggregating-based Markov random field, weighted coexpression network analysis, and supervised regulatory network learning. It uses a systems pharmacology approach to infer the combinatorial drug efficacies and synergy mechanisms through drug functional module-induced regulation of target expression analysis. Application of our tool on diffuse large B-cell lymphoma and prostate cancer demonstrated how synergistic drug combinations can be discovered to inhibit multiple driver signaling pathways. Compared to existing computational approaches, DrugComboExplorer had higher prediction accuracy based on in vitro experimental validation and probability concordance index. These results demonstrate that our network-based drug efficacy screening approach can reliably prioritize synergistic drug combinations for cancer and uncover potential mechanisms of drug synergy, warranting further studies in individual cancer patients to derive personalized treatment plans.

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 DrugComboExplorer.

Driver Network as a Biomarker: Systematic integration and network modeling of multi-omics data to derive driver signaling pathways for drug combination prediction

System requirements

The minimum of system requirements for DrugComboExplorer

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 DrugComboExplorer on Windows OS

- **Install Java JRE**
  DrugComboExplorer 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

- **Run DrugComboExplorer**
  Decompress DrugComboExplorer.zip

  Double click run_DrugComboExplorer.bat in the DrugComboExplorer folder. The DrugComboExplorer will be opened shown in Figure 1.
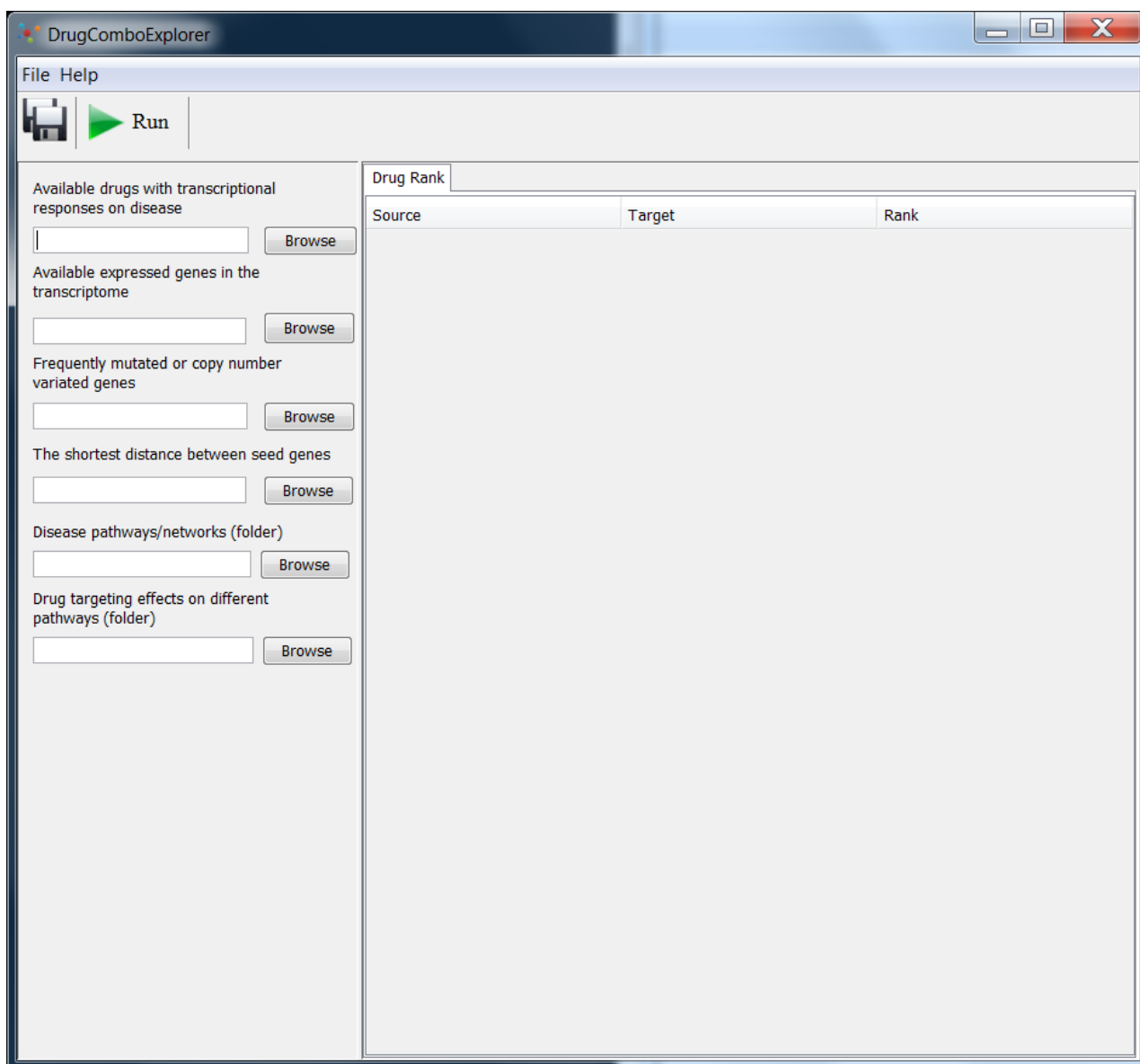
Figure 1

Use the following input files in the sample folder and click RUN button to run the DrugComboExplorer.

File Name	Description	Content
oci_ly3_drug_special_target.txt	Available drugs with transcriptional responses on disease	Lincs database on pathway genes
oci_ly3_gene_expressed.txt	Available expressed genes in the transcriptome	expressed gene id
oci_ly3_pathway_gene_collect_for_seed_genes.txt	Frequently mutated or copy number variated genes	gene id

shortest_path_protein_oci_ly3_seed_genes.txt	the shortest distance between seed genes	the distance of the expressed genes, the matrix value is the distance weight
ly3_signal_info_update_seed	disease pathways/networks	Pathway with the gene id list
oci_ly3_group_pathway_target_effect	Drug targeting effects on different pathways	Lincs database on pathway genes

The DrugComboExplorer will calculate the ranks. The ranks will be listed in the table on the right. (Figure 2).
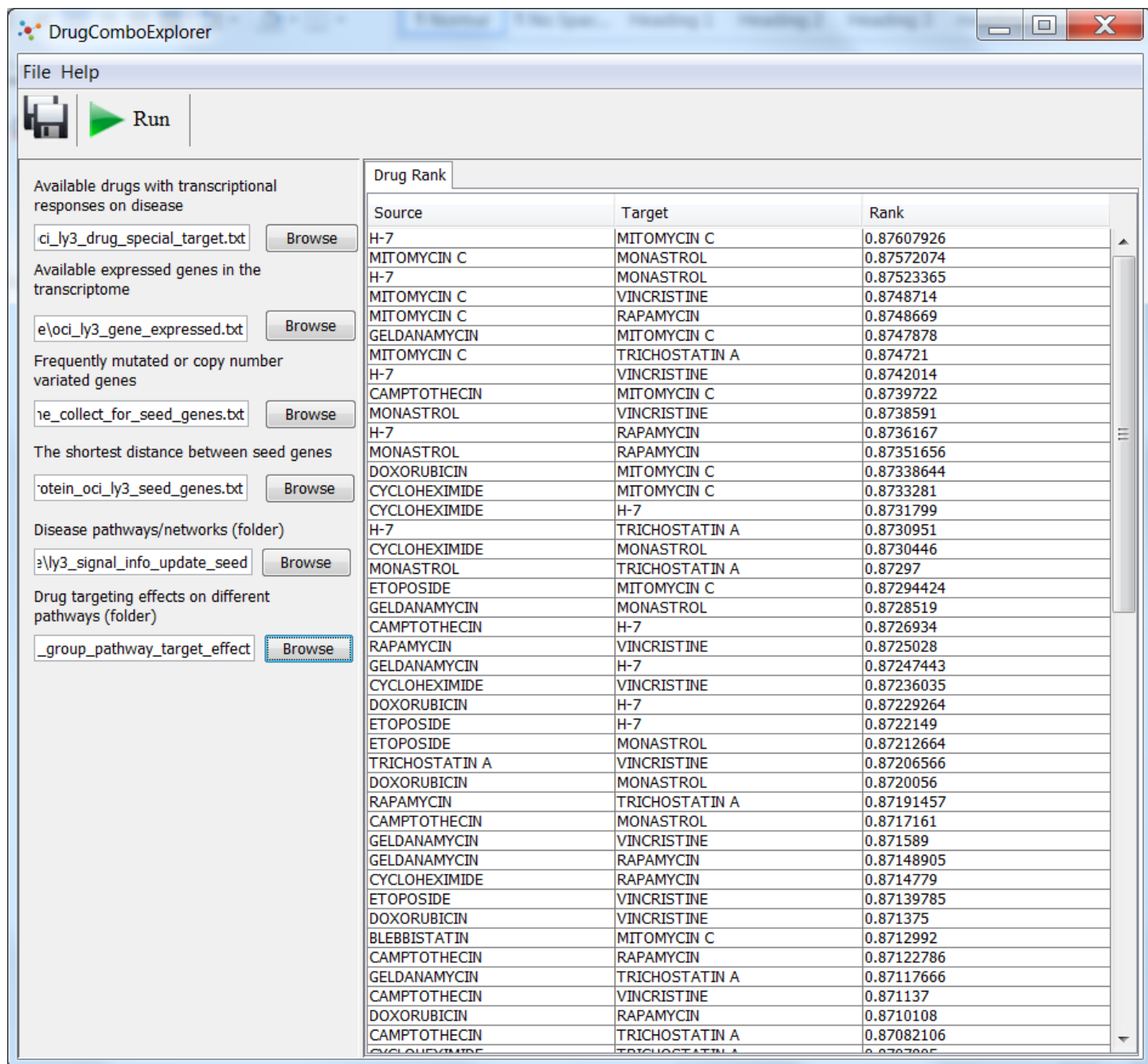
Figure 2

4. Click a row of the table, DrugComboExplorer will display all related pathways. (Figure 3).
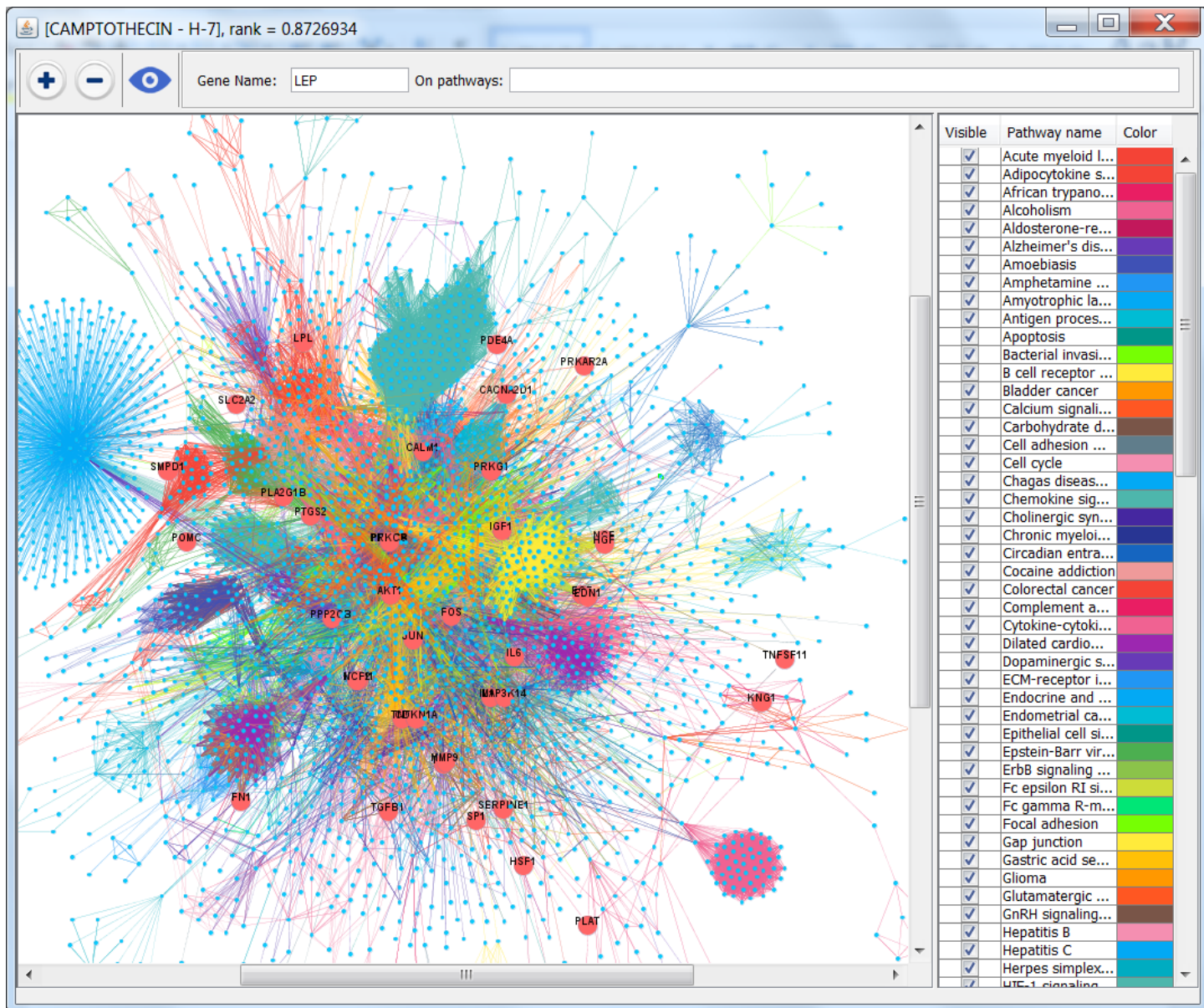
Figure 3

Install and run DrugComboRanker running environment on Ubuntu

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

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

- **Install Python 2.7.x package**

```
sudo apt update

sudo apt upgrade

sudo apt install python2.7 python-pip

sudo apt install python3-pip

sudo apt-get install python-numpy python-scipy python-matplotlib ipython ipython-notebook python-pandas
python-sympy python-nose

cd DrugComboExplorer/networkx2.2

sudo python setup.py install
```

- **Run DrugComboExploer**

  Decompress DrugComboRanker.zip

```
unzip  DrugComboExplorer_Linux.zip
```

  In the DrugComboExplorer folder, run the following command to open DrugComboExplorer as Figure 4
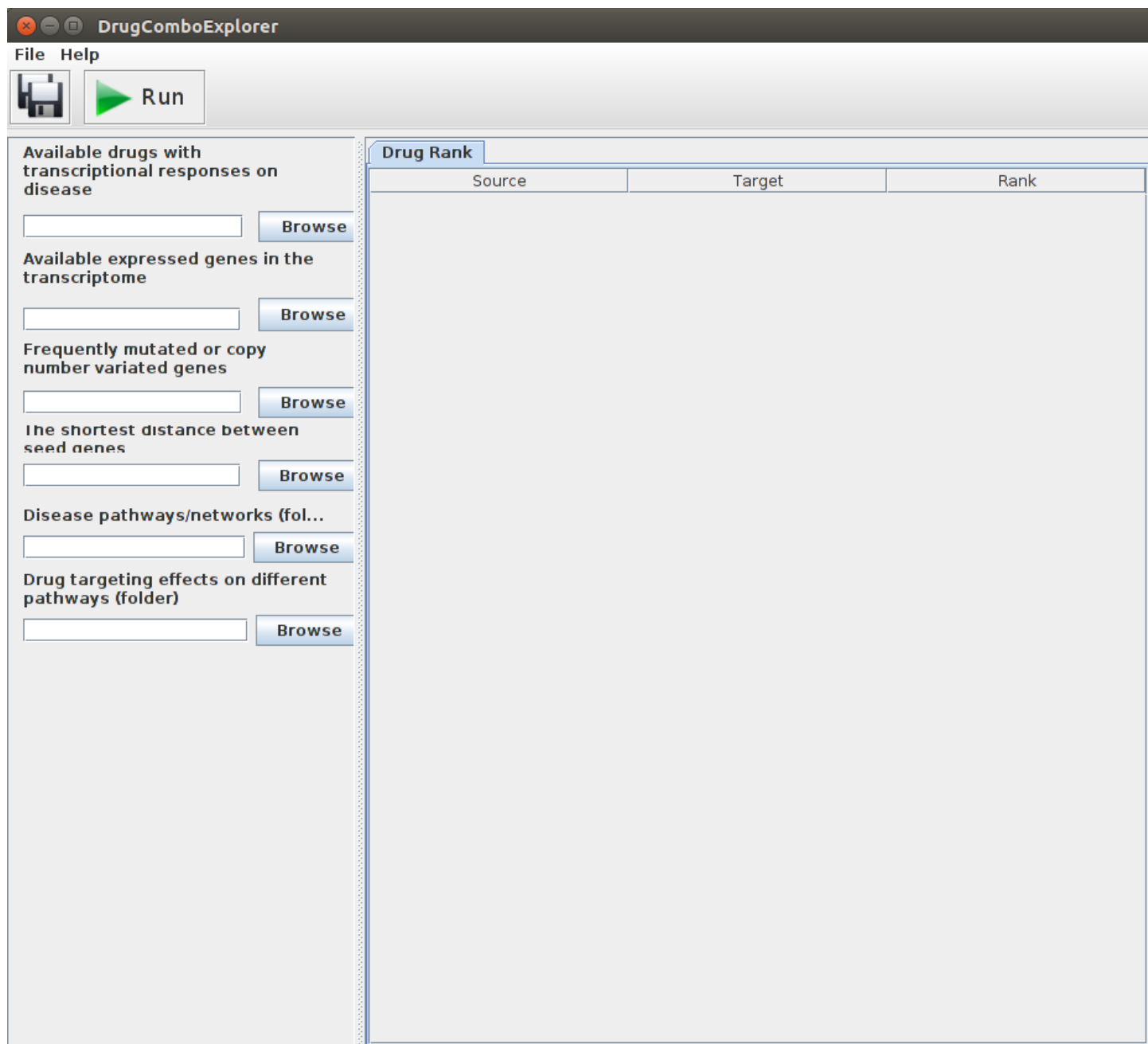
```
./run_DrugComboExplorer.sh
```

Figure 4

Use the following input files in the sample folder and click RUN button to run the DrugComboExplorer.

File Name	Description	Content
oci_ly3_drug_special_target.txt	Available drugs with transcriptional responses on disease	Lincs database on pathway genes

oci_ly3_gene_expressed.txt	Available expressed genes in the transcriptome	expressed gene id
oci_ly3_pathway_gene_collect_for_seed_genes.txt	Frequently mutated or copy number variated genes	gene id
shortest_path_protein_oci_ly3_seed_genes.txt	the shortest distance between seed genes	the distance of the expressed genes, the matrix value is the distance weight
ly3_signal_info_update_seed	disease pathways/networks	Pathway with the gene id list
oci_ly3_group_pathway_target_effect	Drug targeting effects on different pathways	Lincs database on pathway genes

The DrugComboExplorer will calculate the ranks. The ranks will be listed in the table on the right. (Figure 5).

Figure 5