MANTRA 2.0 TUTORIAL

mantra.tigem.it

OUTLINE

1. MANTRA Web Tool
2. Analysis
   a) New Experiment
   b) New Node
   c) GSEA
3. Network
   a) View
   b) Button Panel
4. Search
5. In Summary
6. Conclusion

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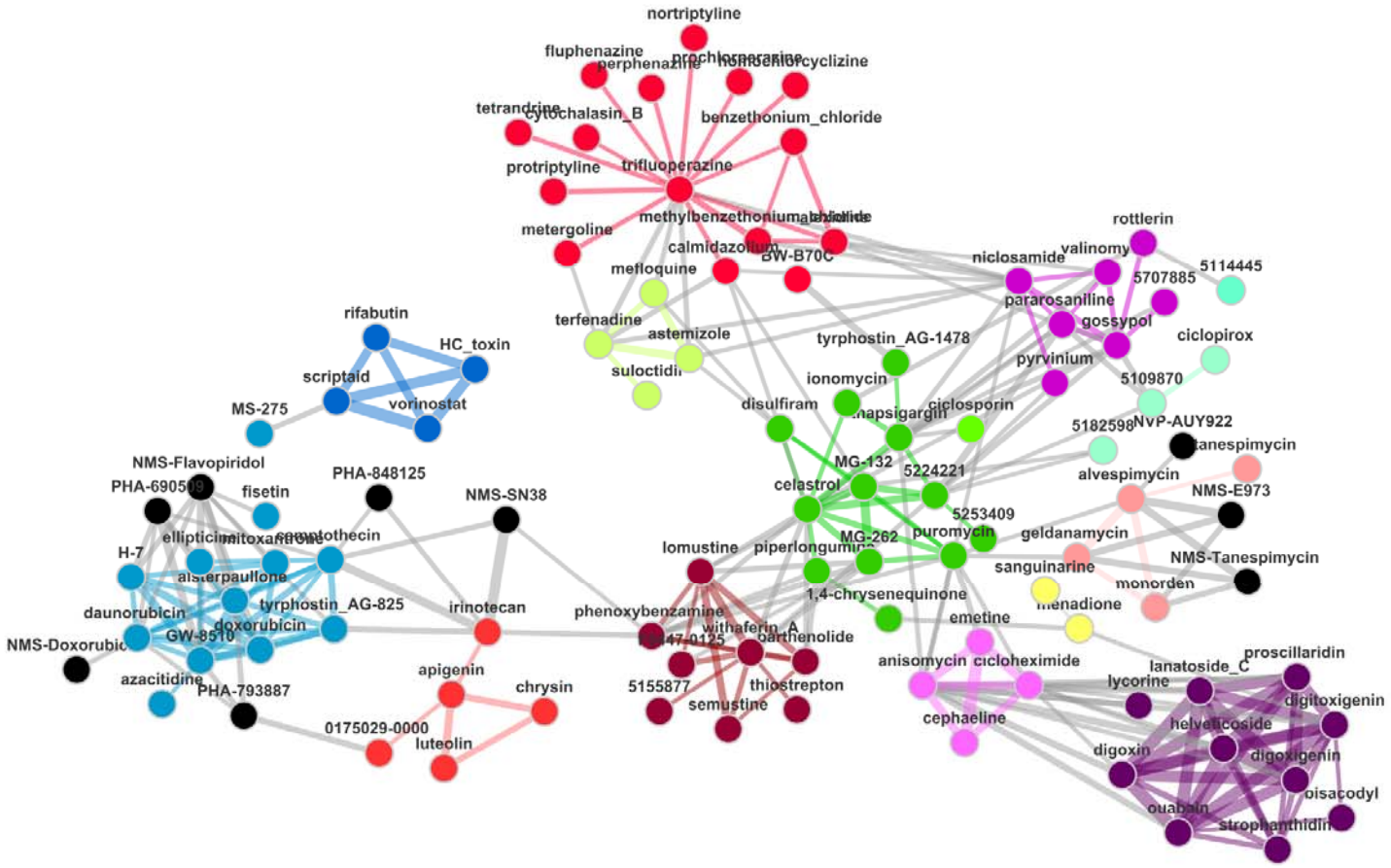
MANTRA WEB TOOL

MANTRA (Mode of Action by NeTwoRk Analysis) is a software tool for the analysis of the Mode of Action (MoA) of drugs and for “drug repositioning”. It is based on network theory and non-parametric statistics on gene expression data.



MANTRA WEB TOOL - Mantra 2.0 Features

1. Database for add and storage of experiments, nodes, and distance matrix
2. Annotation and editing tools for nodes
3. Deleting nodes
4. Integration of a pipeline of microarray analysis
5. Downloading tabulated results and Cytoscape file (.sif format)
6. Common genes analysis
7. Advanced search for nodes
8. Gene set enrichment analysis

MANTRA WEB TOOL - Mantra 2.0 Features

- MANTRA 2.0 has been implemented by customizing the Applet version of Medusa (Hooper and Bork, 2005), a front end for protein interaction databases, which can be also used as a general graph visualization tool.

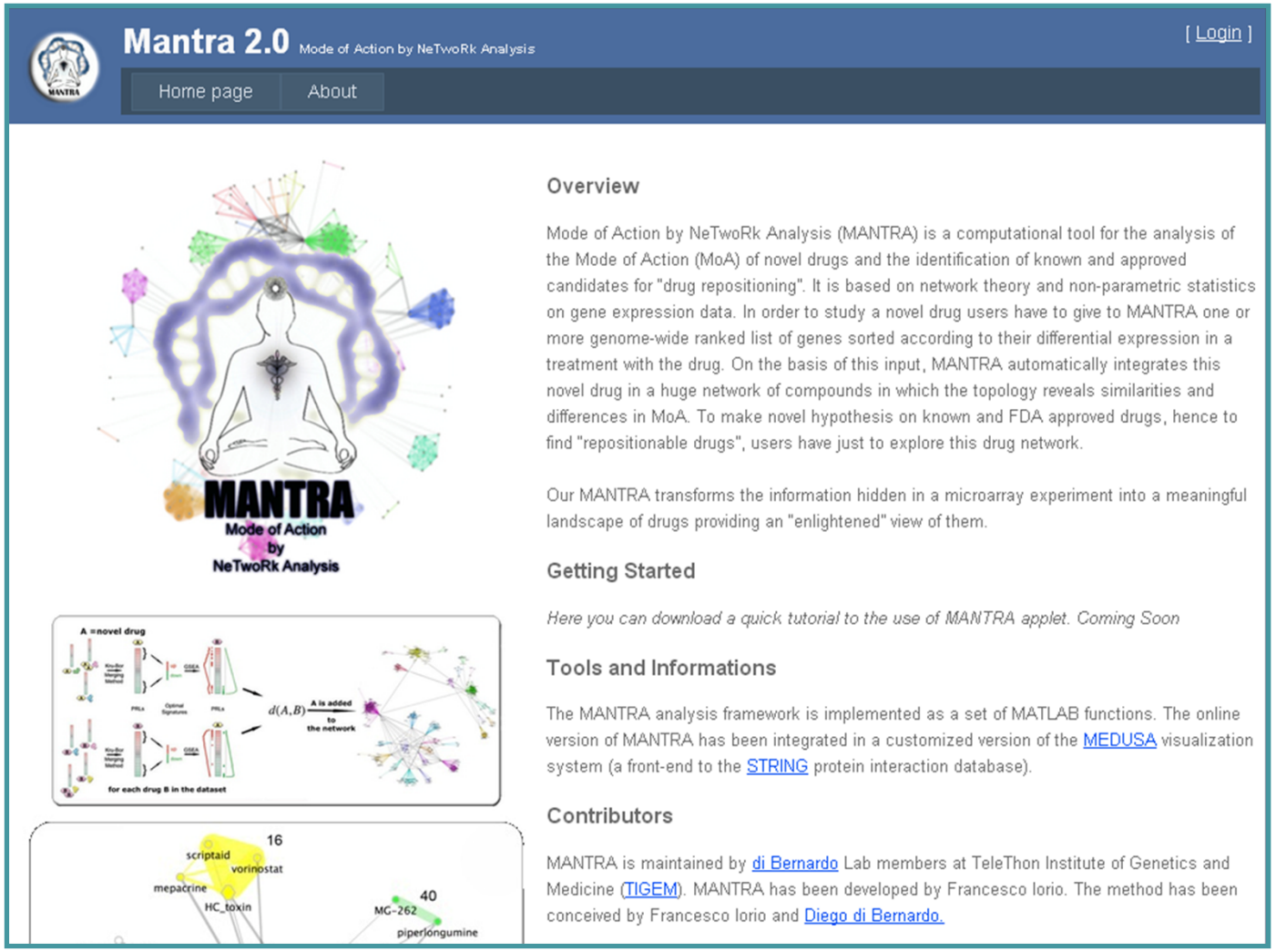
- The MANTRA 2.0 implements the method in (Iorio, et al., 2010) for the discovery of drug MoA and the repositioning of known drugs from the analysis of transcriptional responses.

- It allows users to visually explore the Drug Network that we inferred for 1309 compounds in a user-friendly environment providing, for each of the drugs, information about biochemical interactions, therapeutic indications, known MoA, pharmacology and targeted proteins.

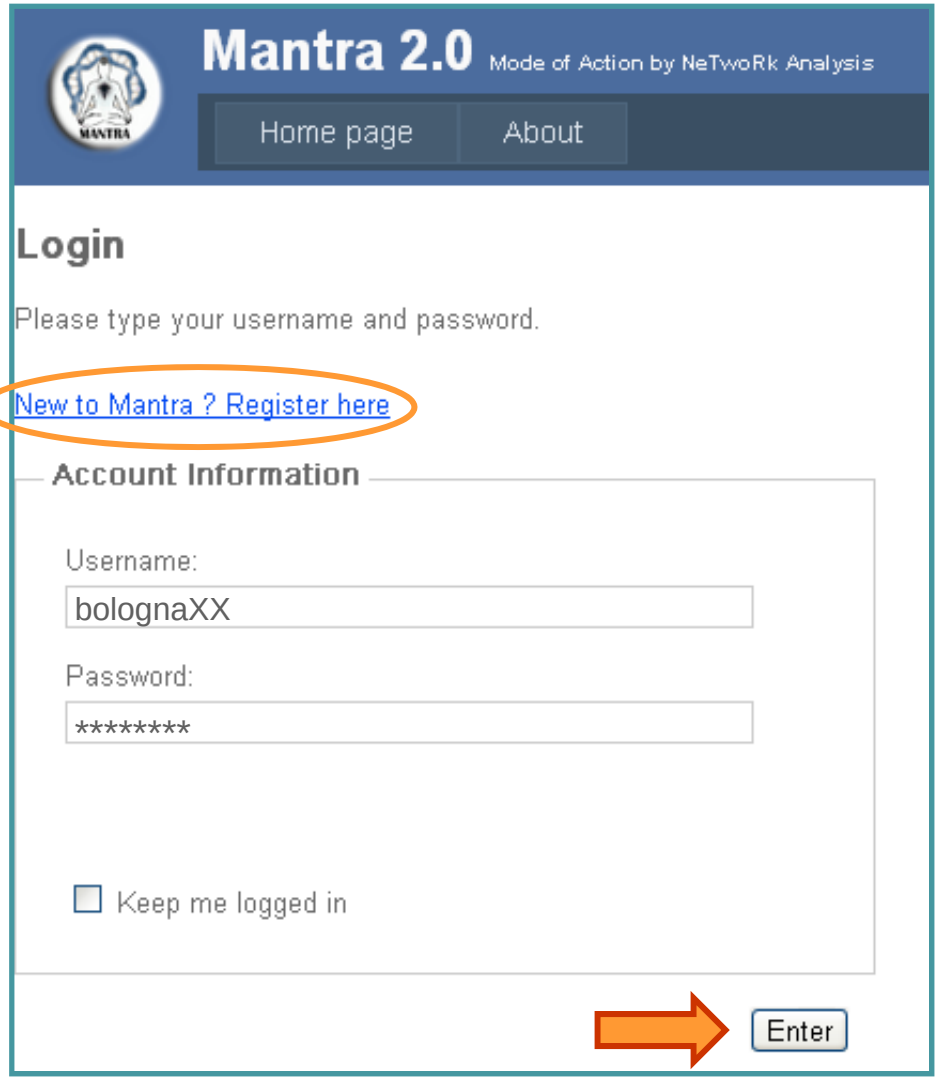
- By exploring the Drug Network, users can identify unexpected similarities between drugs acting on different direct intra-cellular targets and search for “repositionable” drugs.

MANTRA WEB TOOL - Register and login

To access the web-tool click on "**Login**" in top right.



MANTRA WEB TOOL - Register and login



1. If you are not registered, click on "**New to Mantra ? Register here**";

2. After filling in the registration form, you will receive an email with a link to activate your account;

3. Access to the web tool with your username and password;

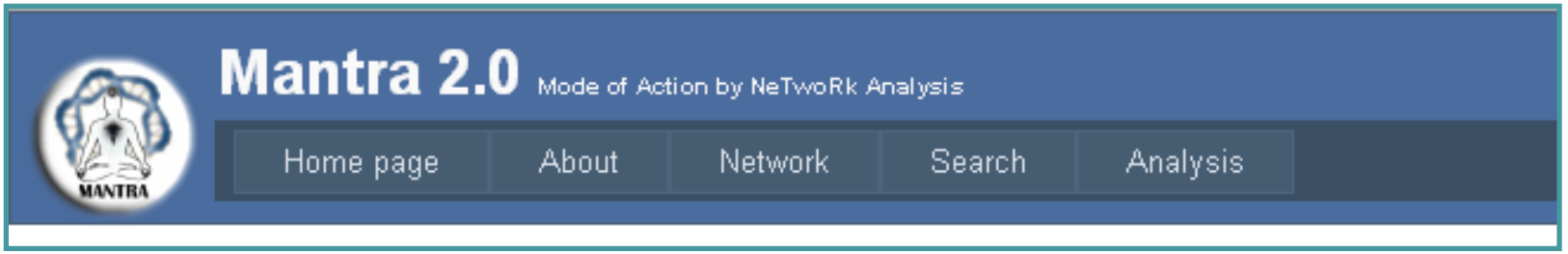
4. At last, click on ''**Enter**''.

MANTRA WEB TOOL - Workspaces

Our web tool consists of three different workspaces:

a) Analysis
b) Network
c) Search

Each of these workspaces can be selected, after login, by clicking on the respective tab.



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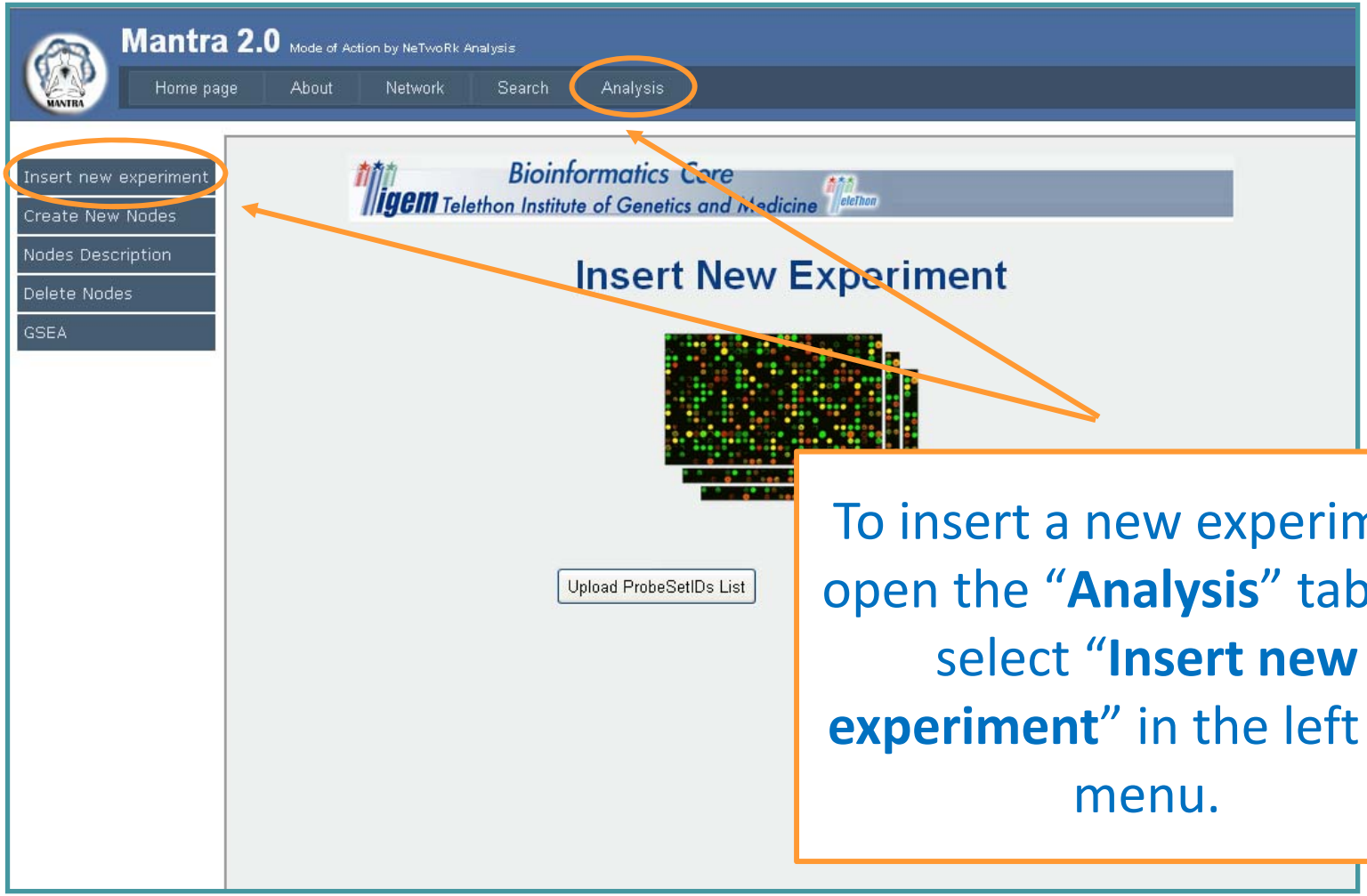
NEW EXPERIMENT

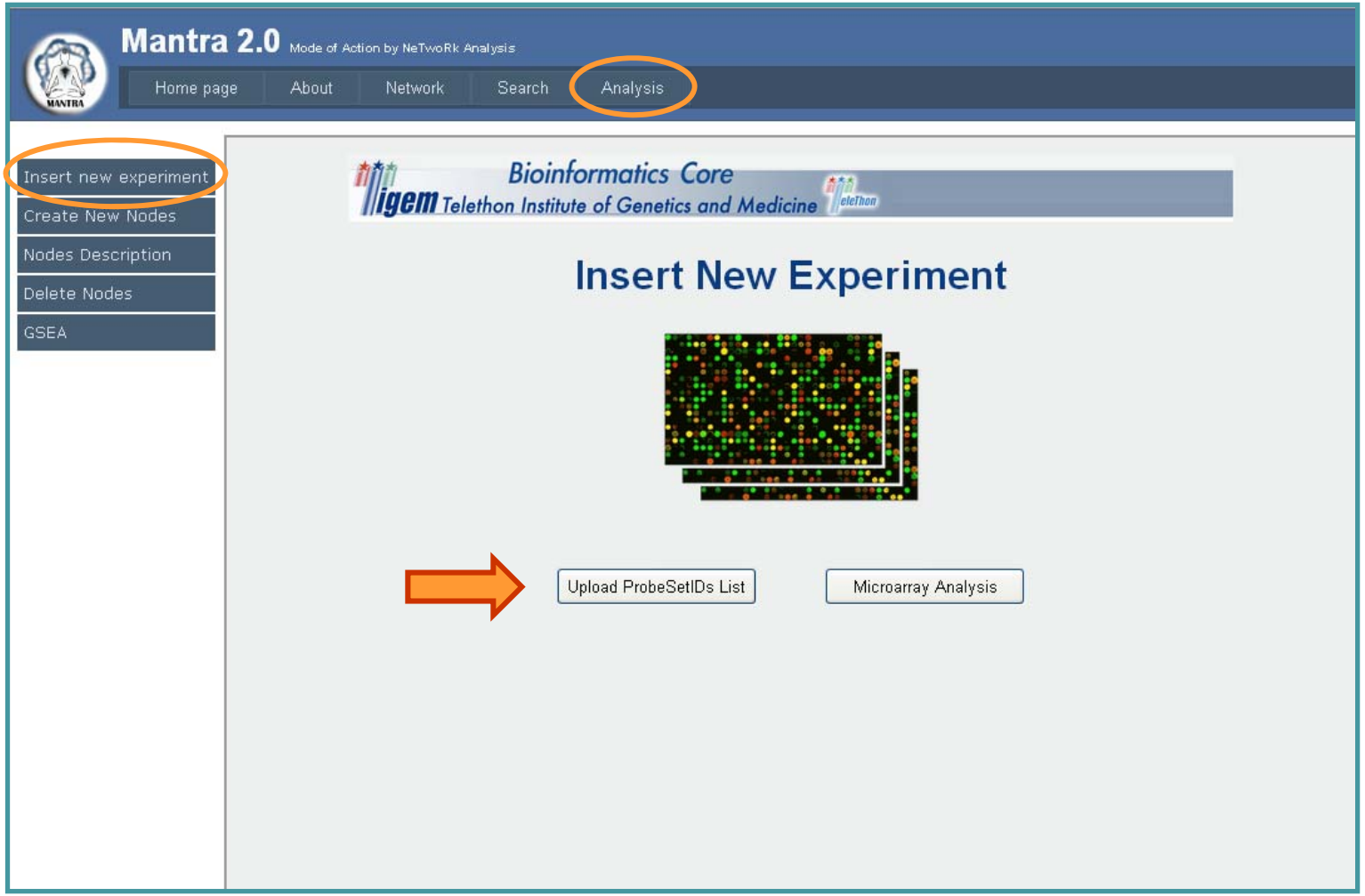
A user can choose to integrate its own drug in the Network and to classify its MoA by uploading ranked lists of Affymetrix probes or raw data of Affymetrix chips on our server.



To insert a new experiment open the "**Analysis**" tab and select "**Insert new experiment**" in the left side menu.

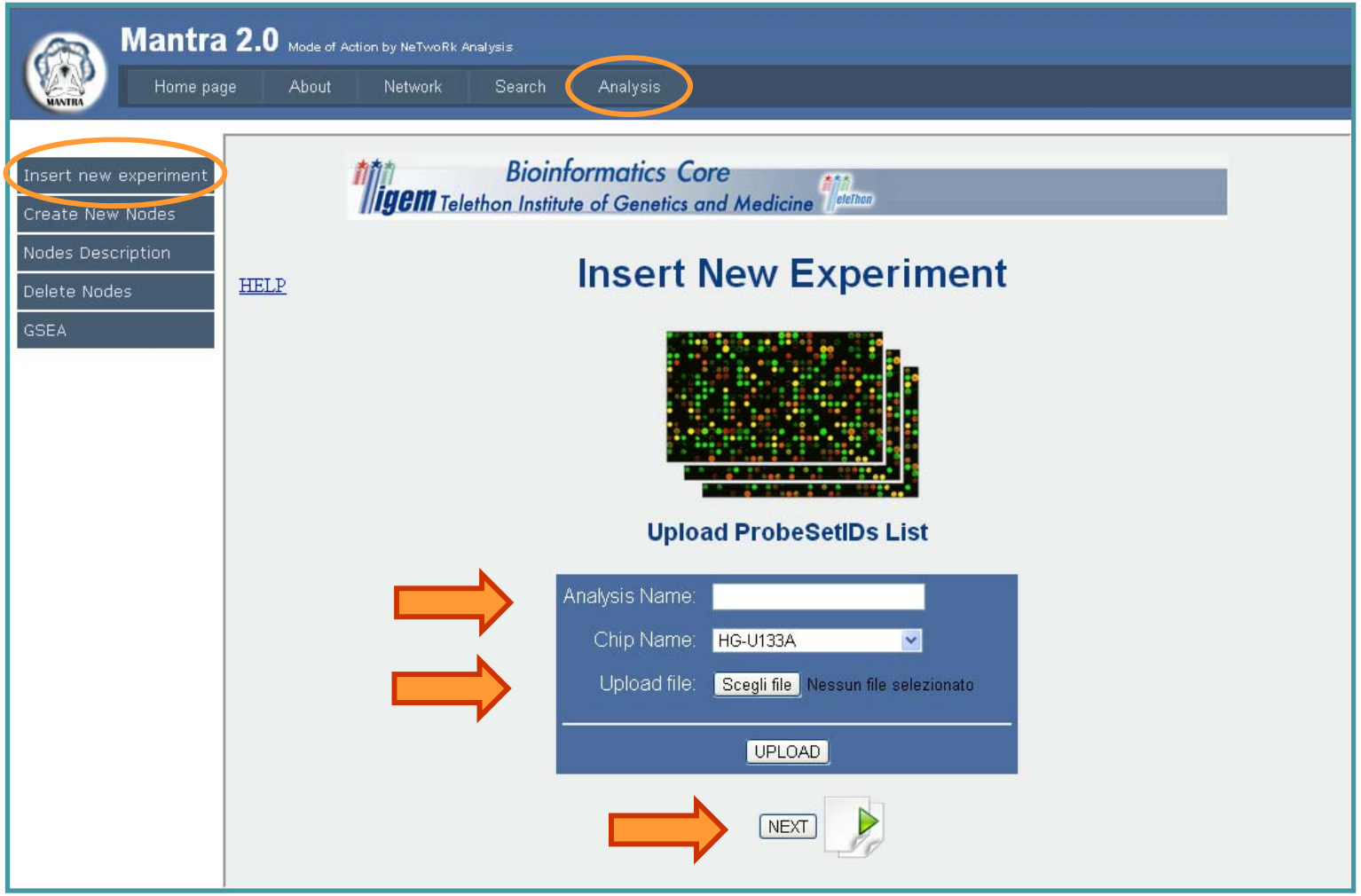
NEW EXPERIMENT - Upload Probes List

To upload a probes list click on "**Upload ProbeSetIDs List**" button.



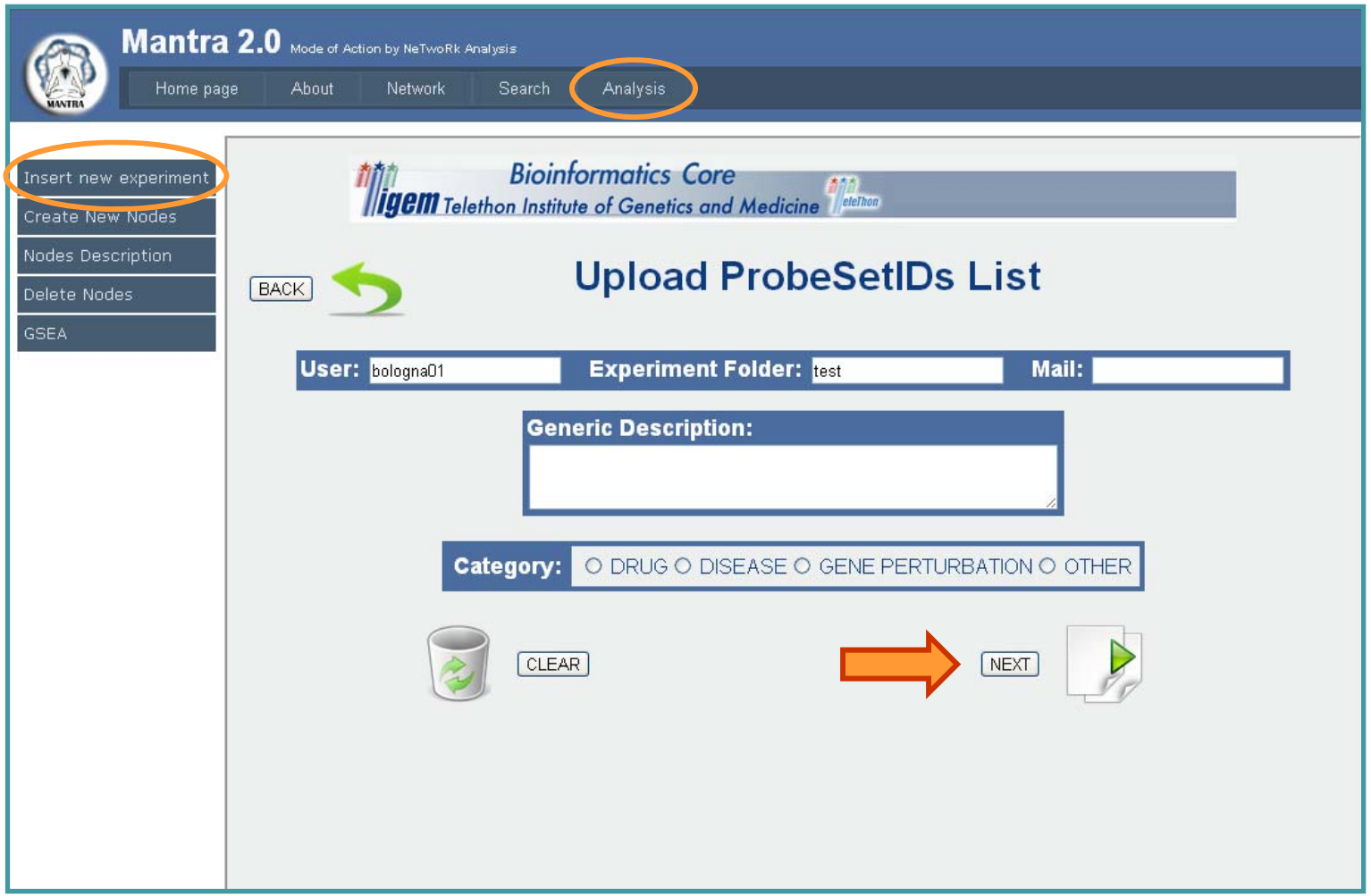
NEW EXPERIMENT - Upload Probes List

Enter “Analysis Name”, “Chip Name” and select a .txt file, containing all the affymetrix probe-set identifiers sorted according to their differential expression following treatment with the testing drug.



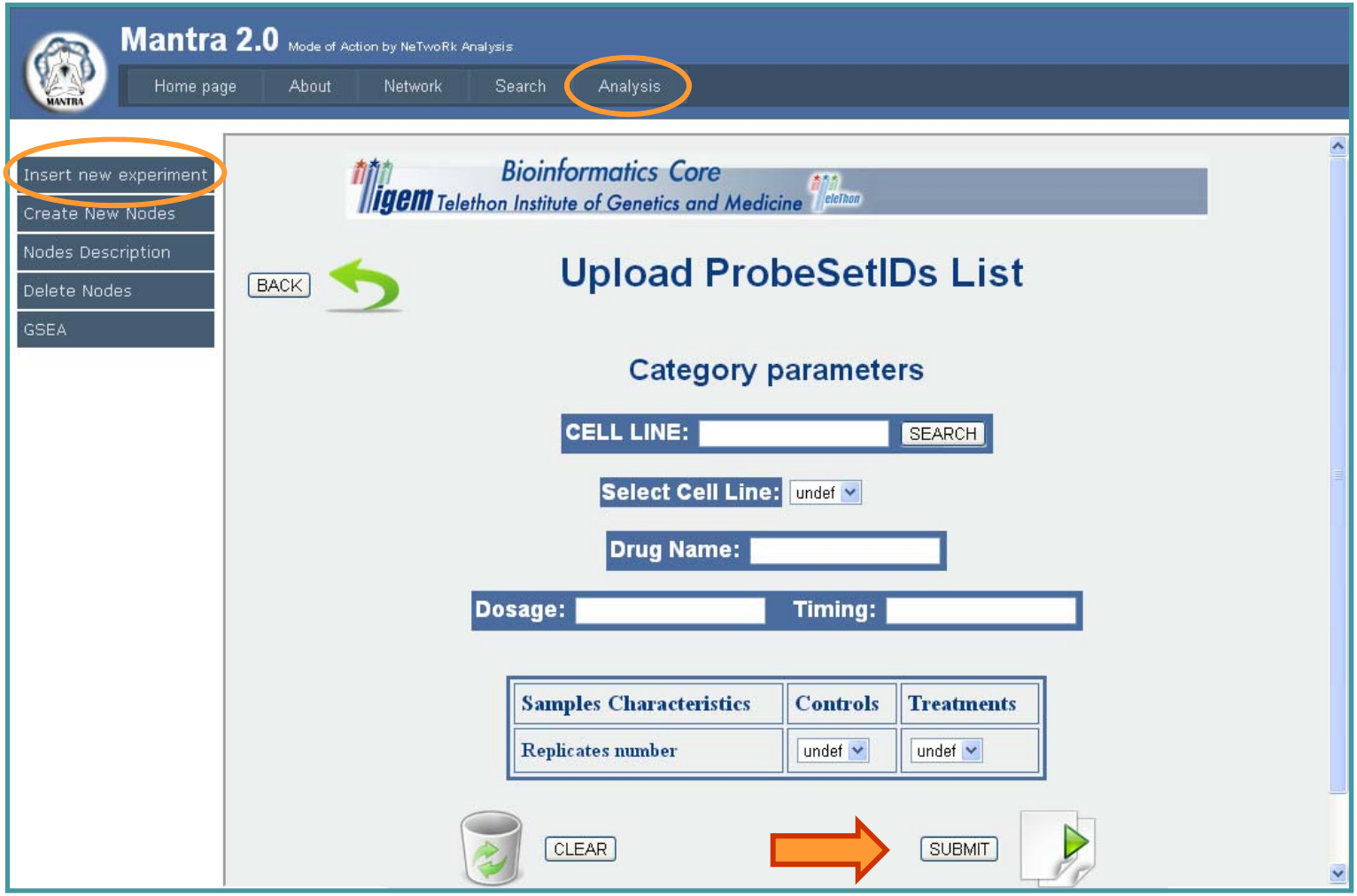
NEW EXPERIMENT - Upload Probes List

Fill some required fields (such as Mail, Generic Description and Category) and click on "**NEXT**".



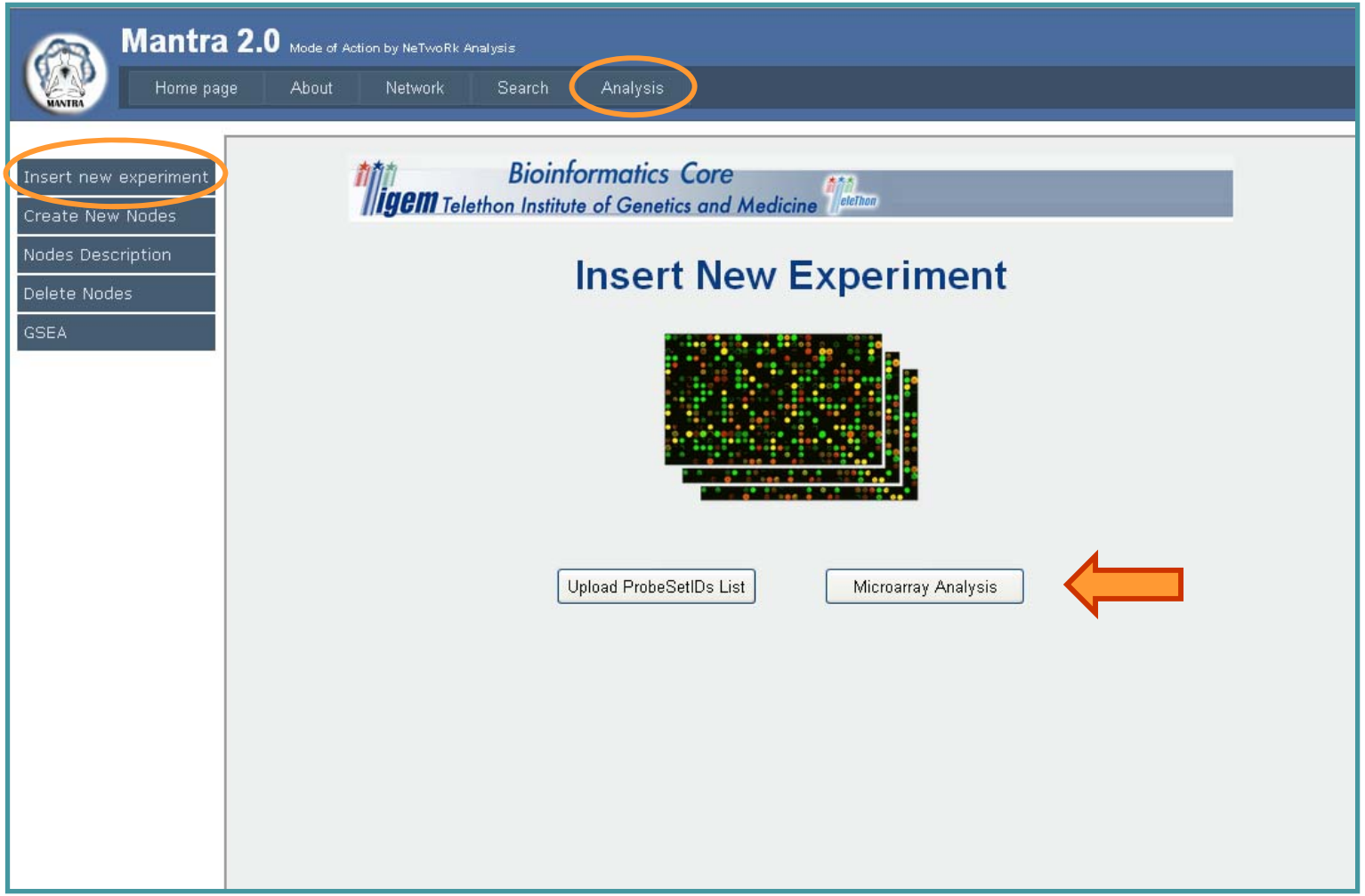
NEW EXPERIMENT - Upload Probes List

Fill some category parameters (such as Cell line, Name, Dosage and Timing, Perturbation Type and Replicates Number) and click on "**SUBMIT**".



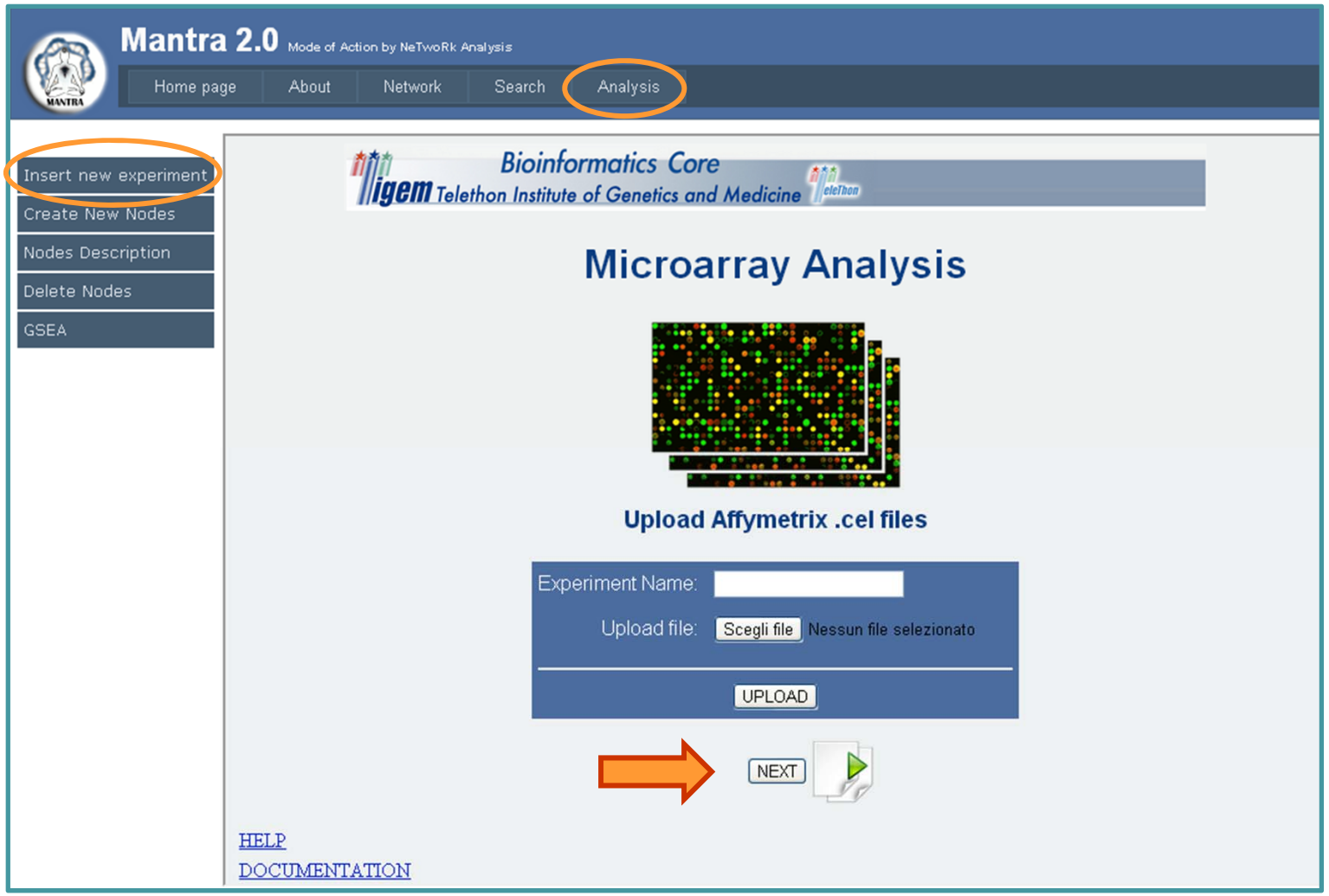
NEW EXPERIMENT - Microarray Analysis

The addition of a Microarray Analysis pipeline allows to analyze raw data from microarray experiments with the Affymetrix platform.
Click on "**Microarray Analysis**" button.



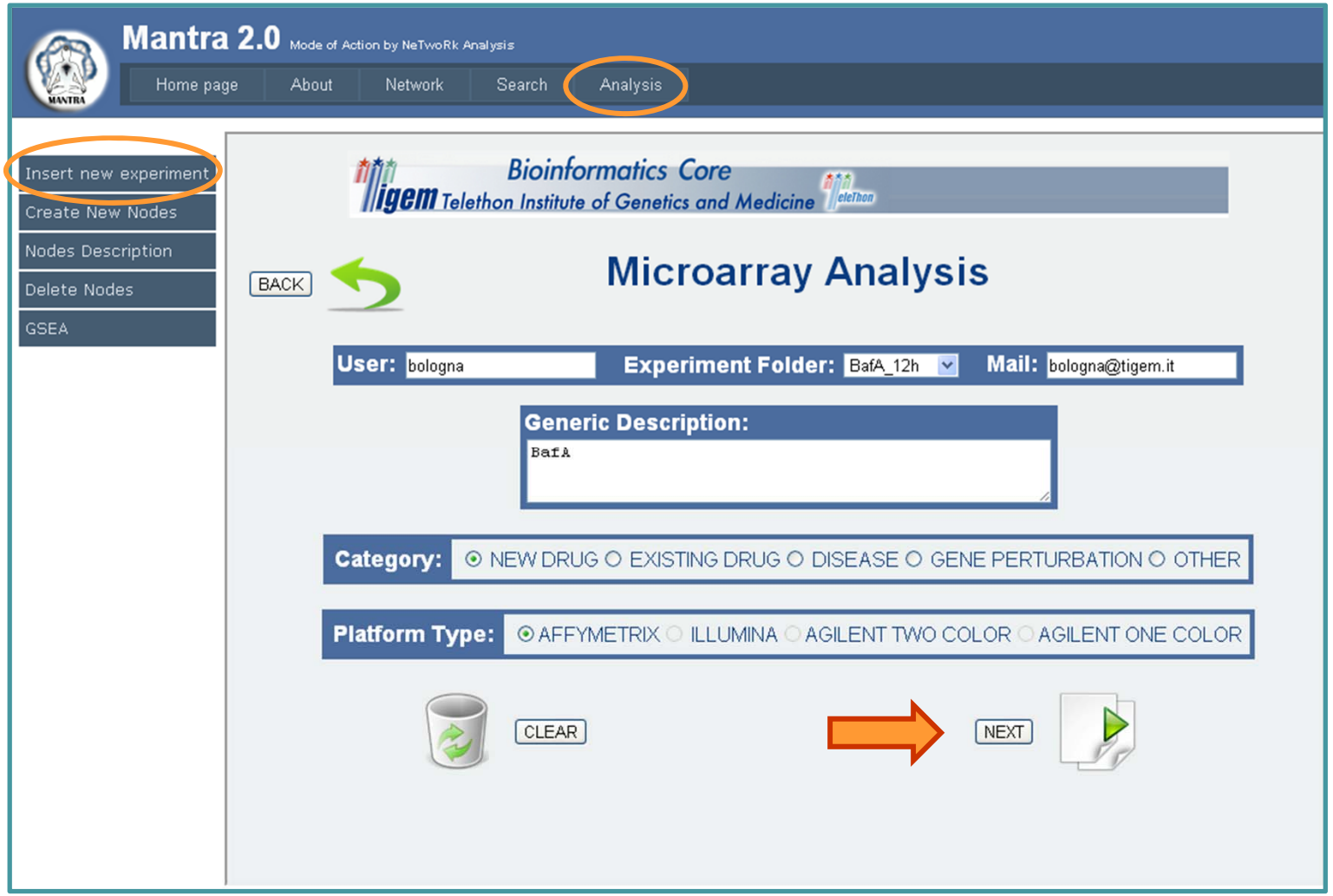
NEW EXPERIMENT - Microarray Analysis

Upload .cel files and click on "**NEXT**".



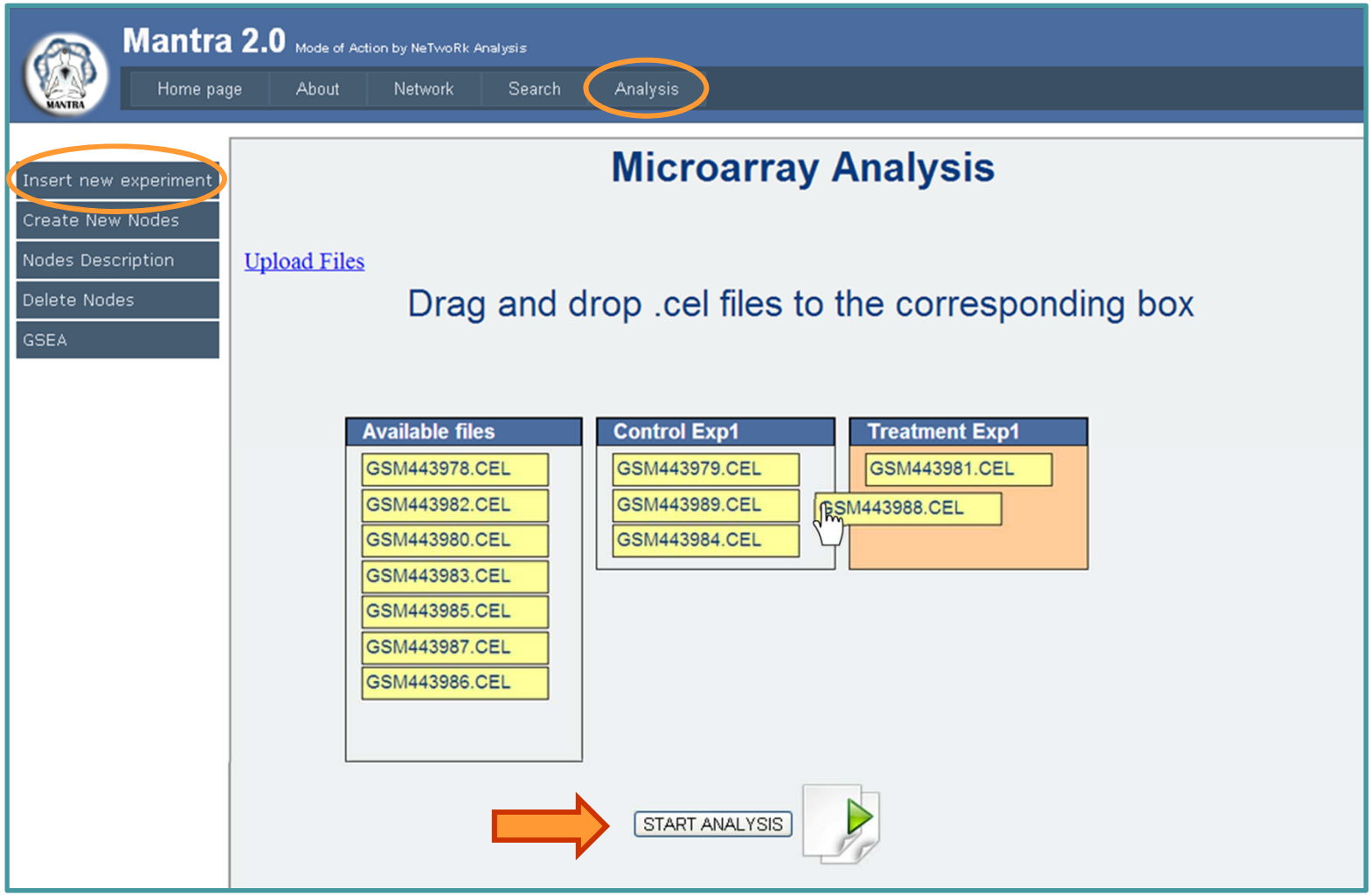
NEW EXPERIMENT - Microarray Analysis

Fill some required fields (such as Mail, Description, Category and Platform Type) and click on "**NEXT**".



NEW EXPERIMENT - Microarray Analysis

Select and load the treated and control files (drag & drop .cel files to the corresponding box) and click on "**START ANALYSIS**".



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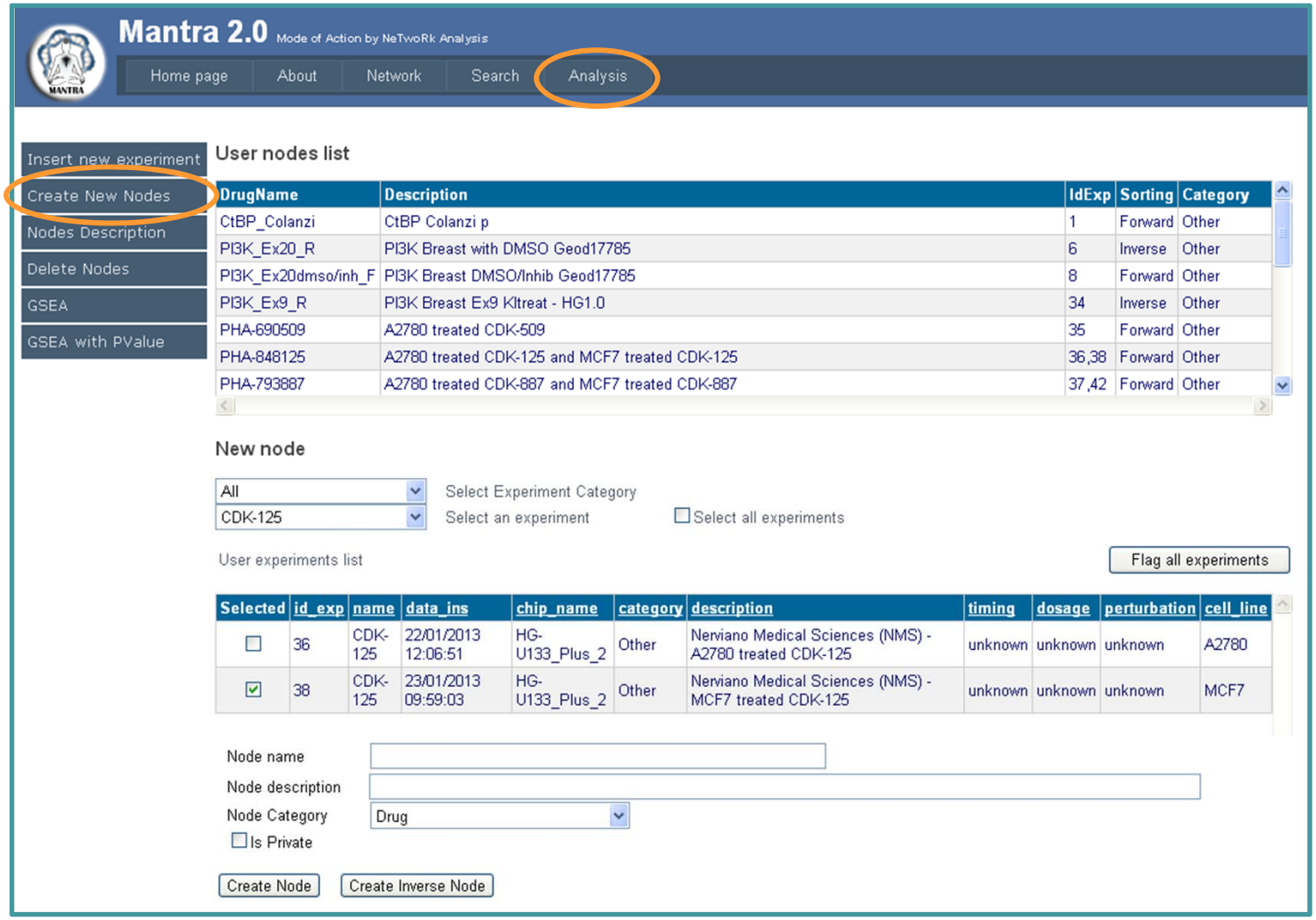
NEW NODE

Selecting from the list the experiments of interest it is possible to extract “K” ordered lists of genes, one for each experiment selected. The “K” lists, appropriately recombined, contribute to the creation of a new node of the drugs network.



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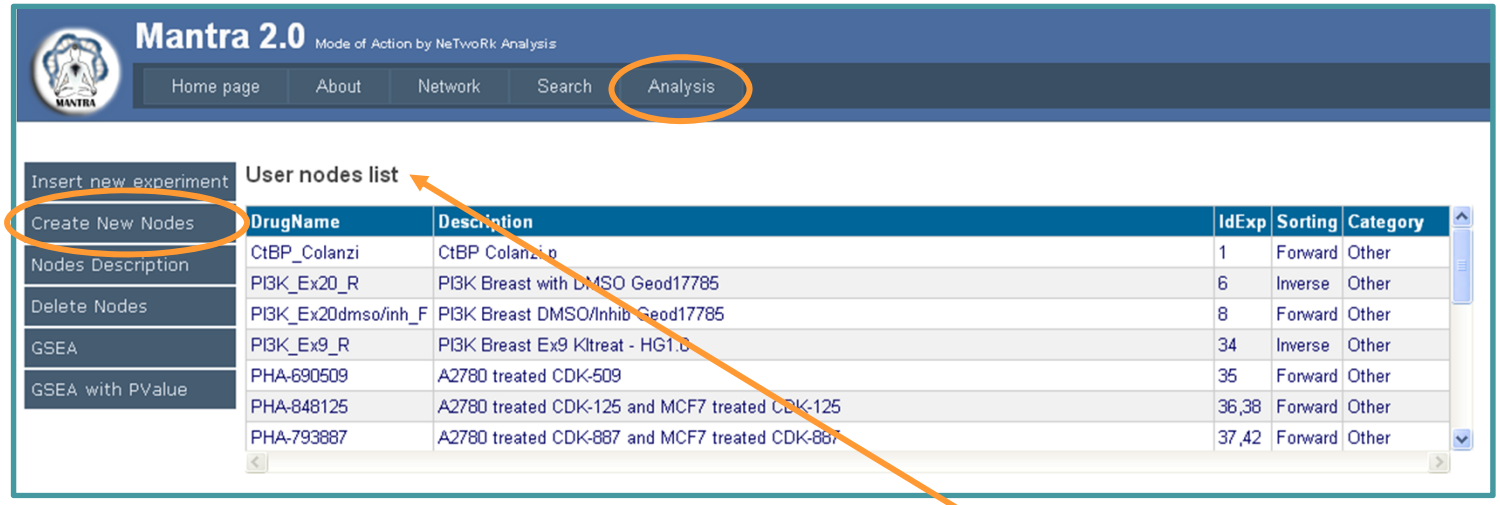


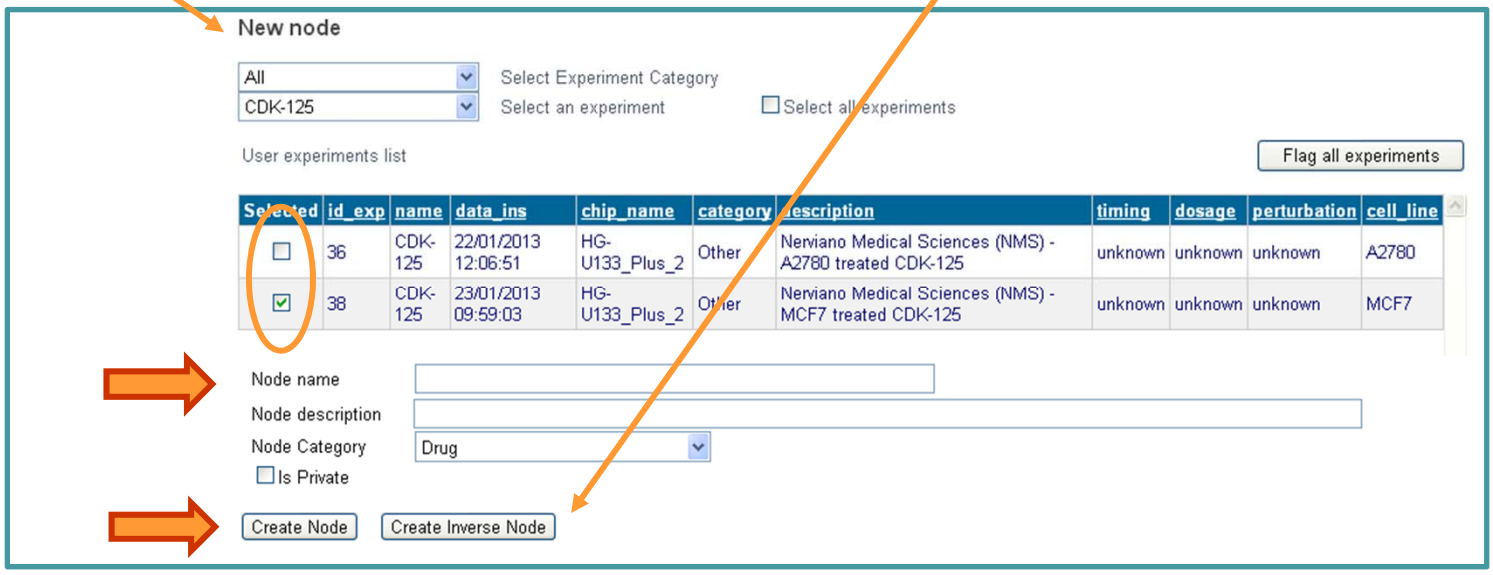
Nodes created by the user

NEW NODE

Selecting from the list the experiments of interest it is possible to extract “K” ordered lists of genes, one for each experiment selected. The “K” lists, appropriately recombined, contribute to the creation of a new node of the drugs network.

Select experiments using the appropriate drop-down menu.
Fill the fields (Name, Description, Category) and click on “**Create Node**” (or "Create Inverse Node").

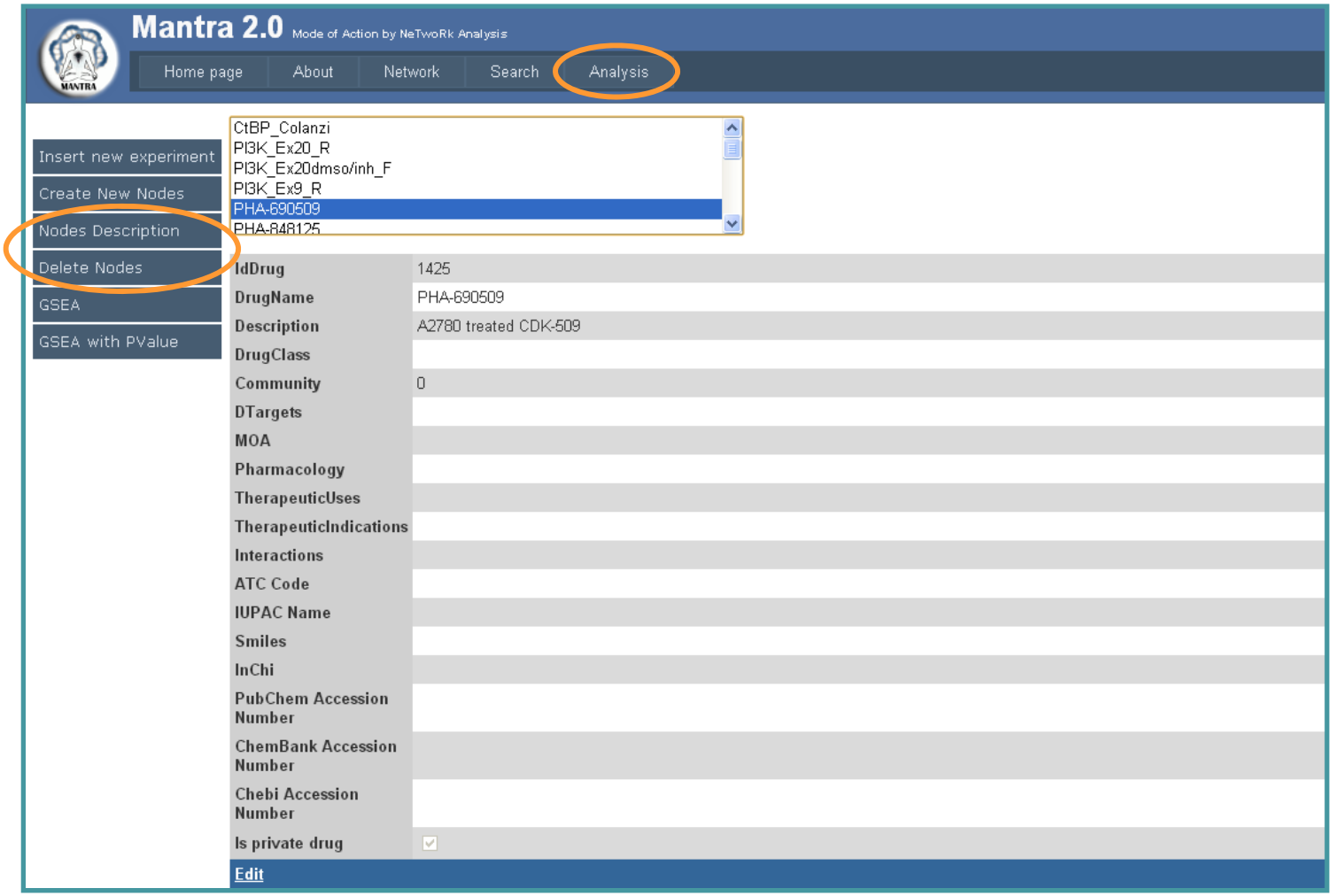
"**Create Inverse Node**": to create ranked list of genes with inverse sorting.



NEW NODE - Editing and Deleting

Two possible operations on the nodes:

1. annotate and edit the details of the user nodes
2. delete the user nodes



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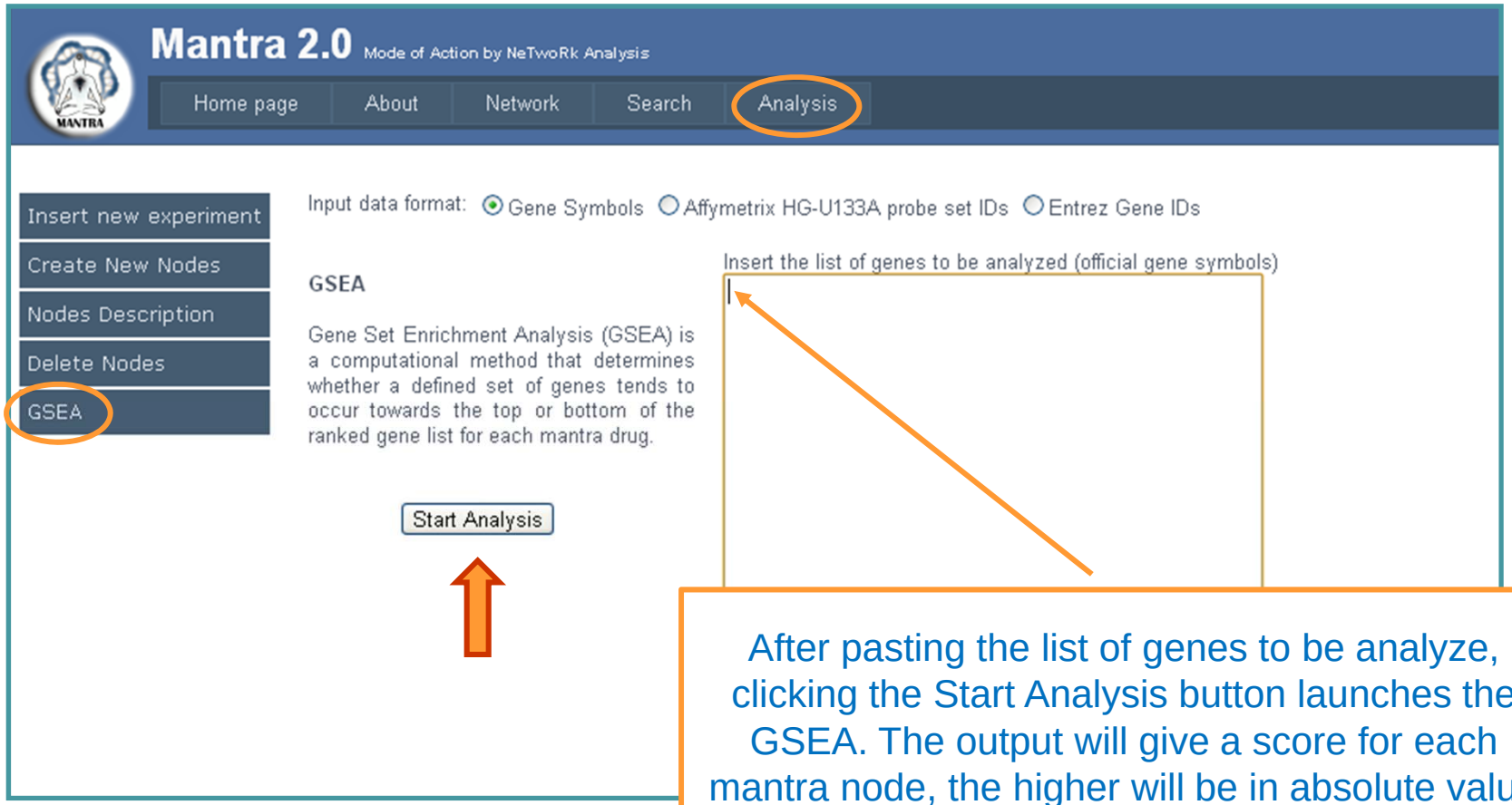
GSEA

Gene Set Enrichment Analysis (GSEA) is a computational method that determines whether a defined set of genes tends to occur towards the top or bottom of the ranked gene list for each mantra drug.



After pasting the list of genes to be analyze, clicking the Start Analysis button launches the GSEA. The output will give a score for each mantra node, the higher will be in absolute value the more the set of genes will be enriched.

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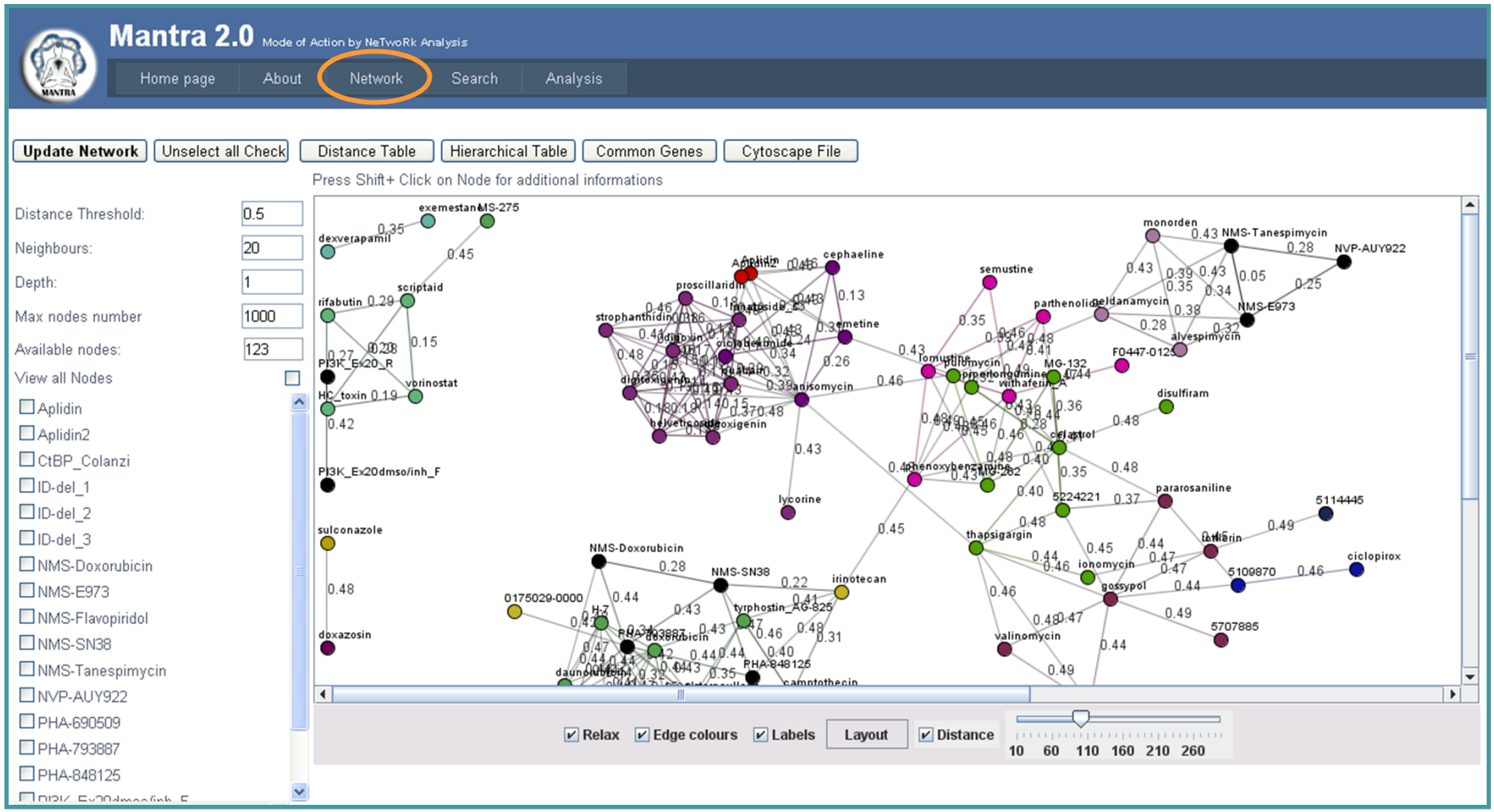
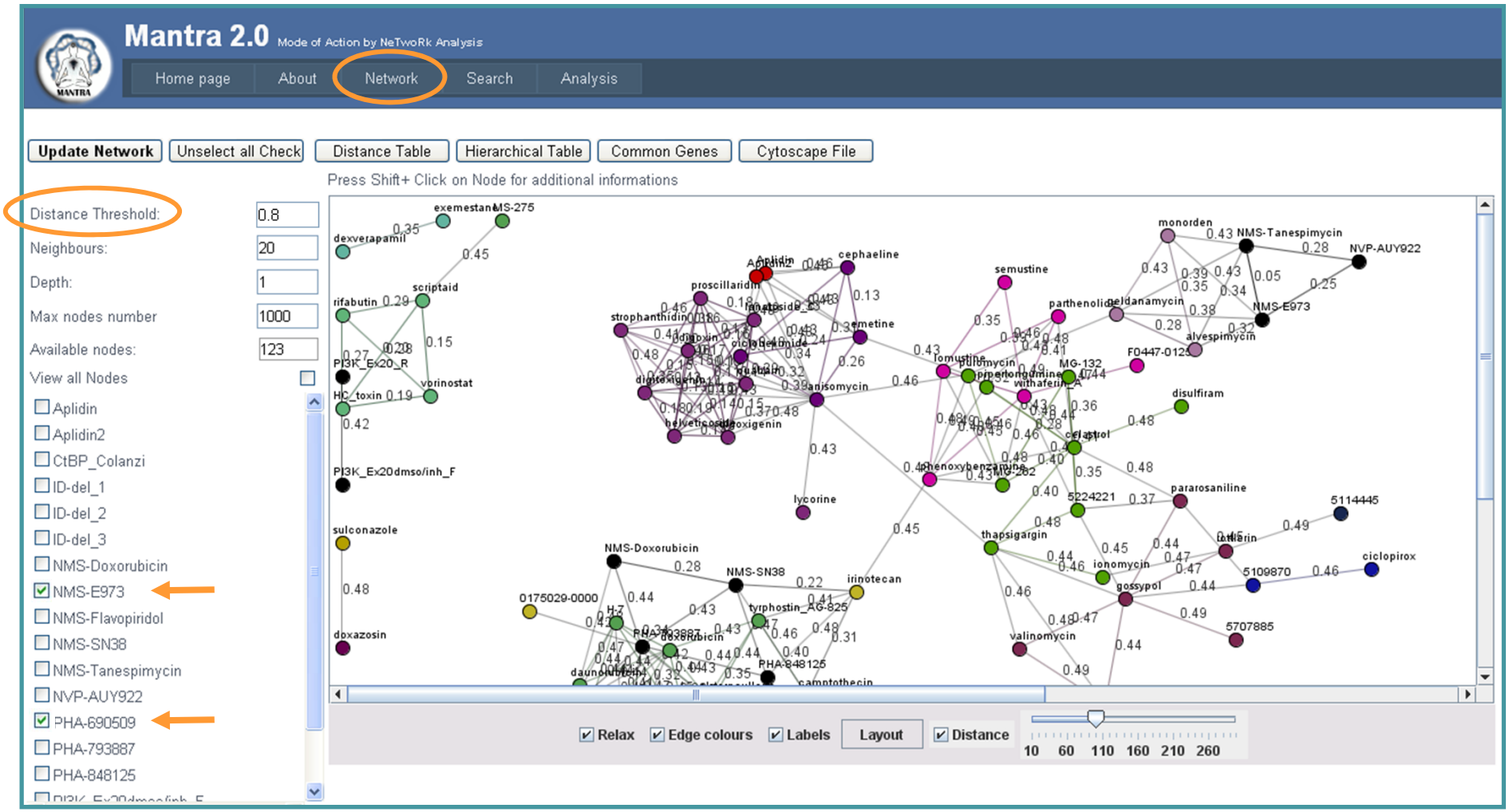
VIEW

The nodes represents the drugs and the edges the distances between them. The drugs belonging to the same community are represented with the same color.



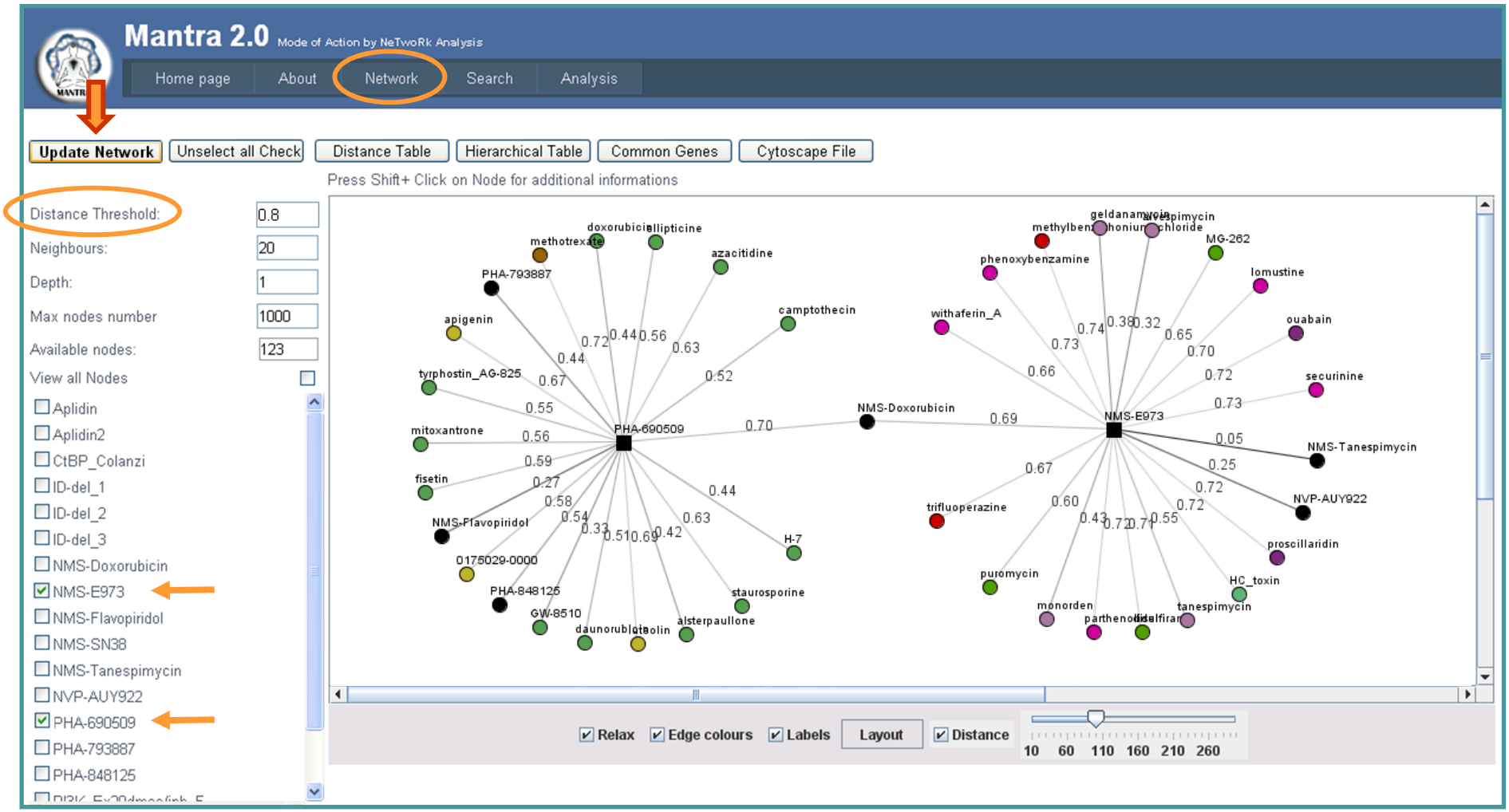
VIEW

The network tab provides a subnet view based on several parameters (distance threshold, the number of neighbors, depth, number max nodes) and according to the selection of one or more nodes available.

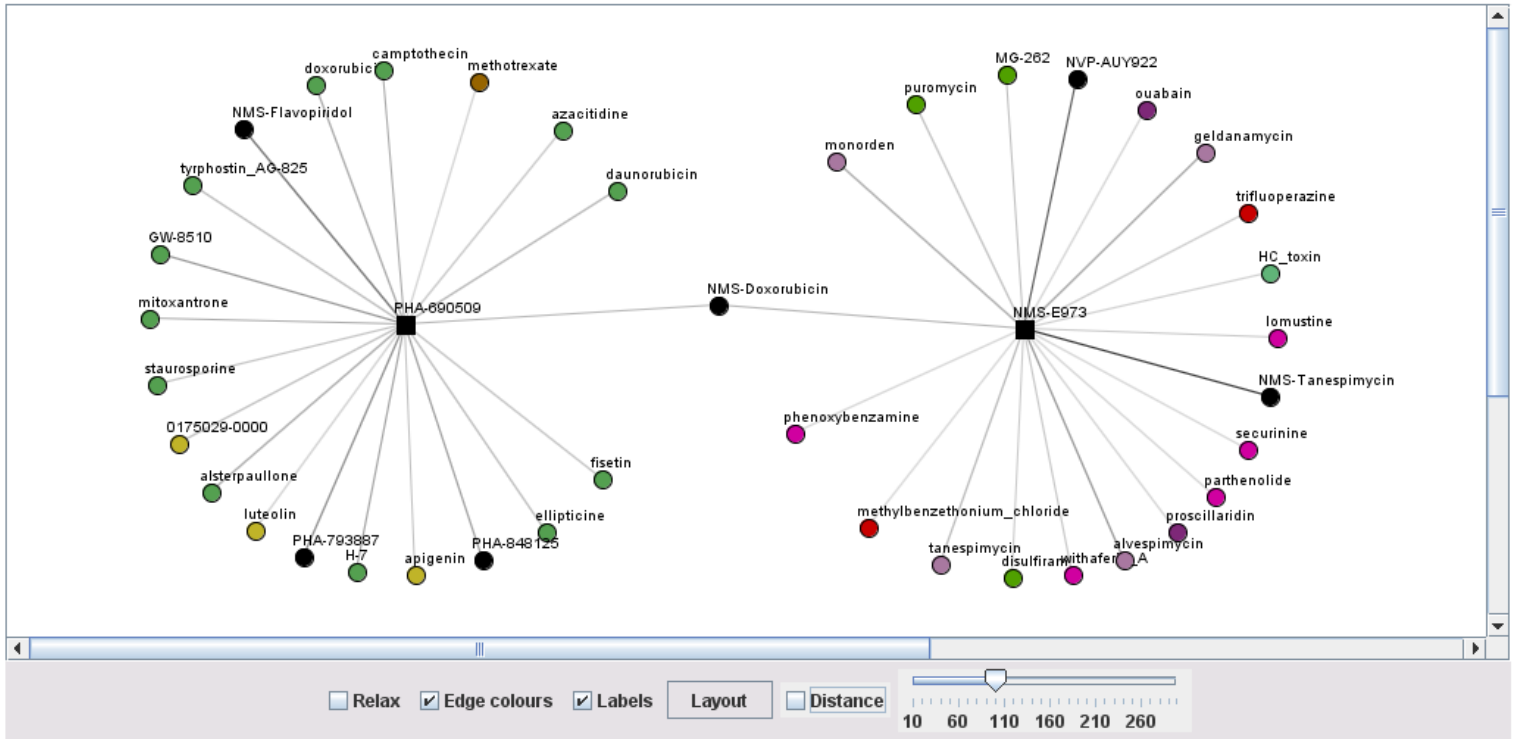


VIEW

Clicking on the “**Update Network**" button will refresh the view.

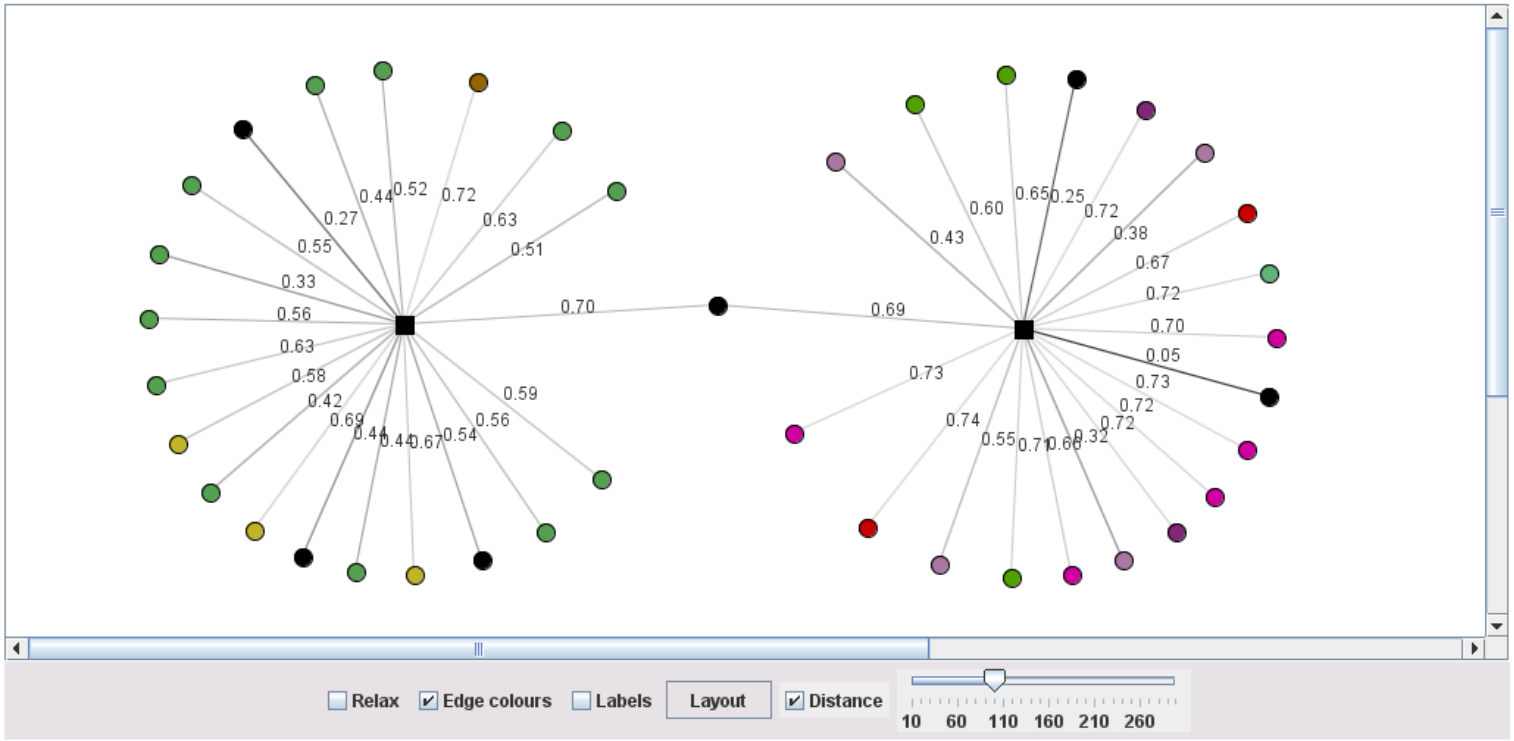


VIEW - Applet Menu: Distance



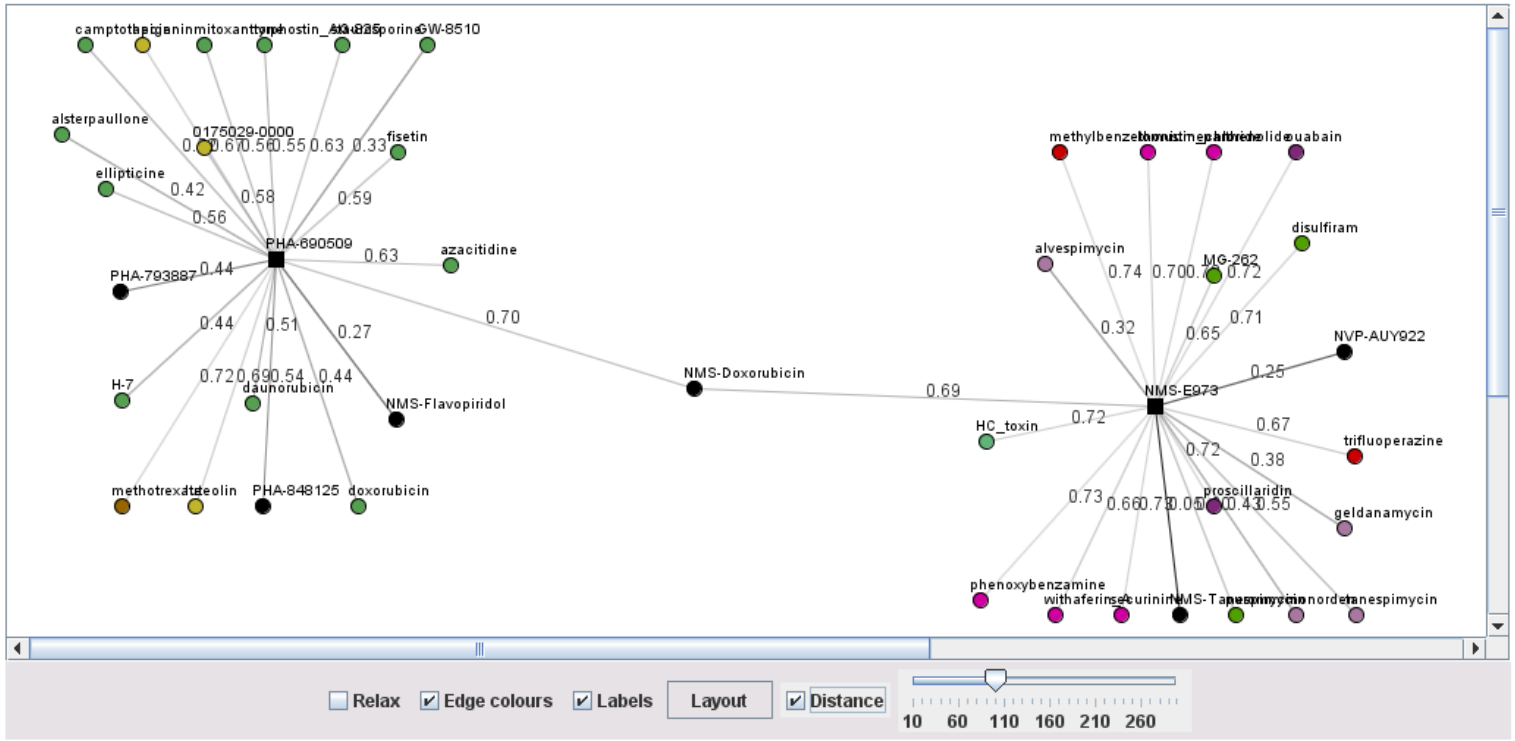
You can unflag "**Distance**" to erase the label of the edges.

VIEW - Applet Menu: Labels



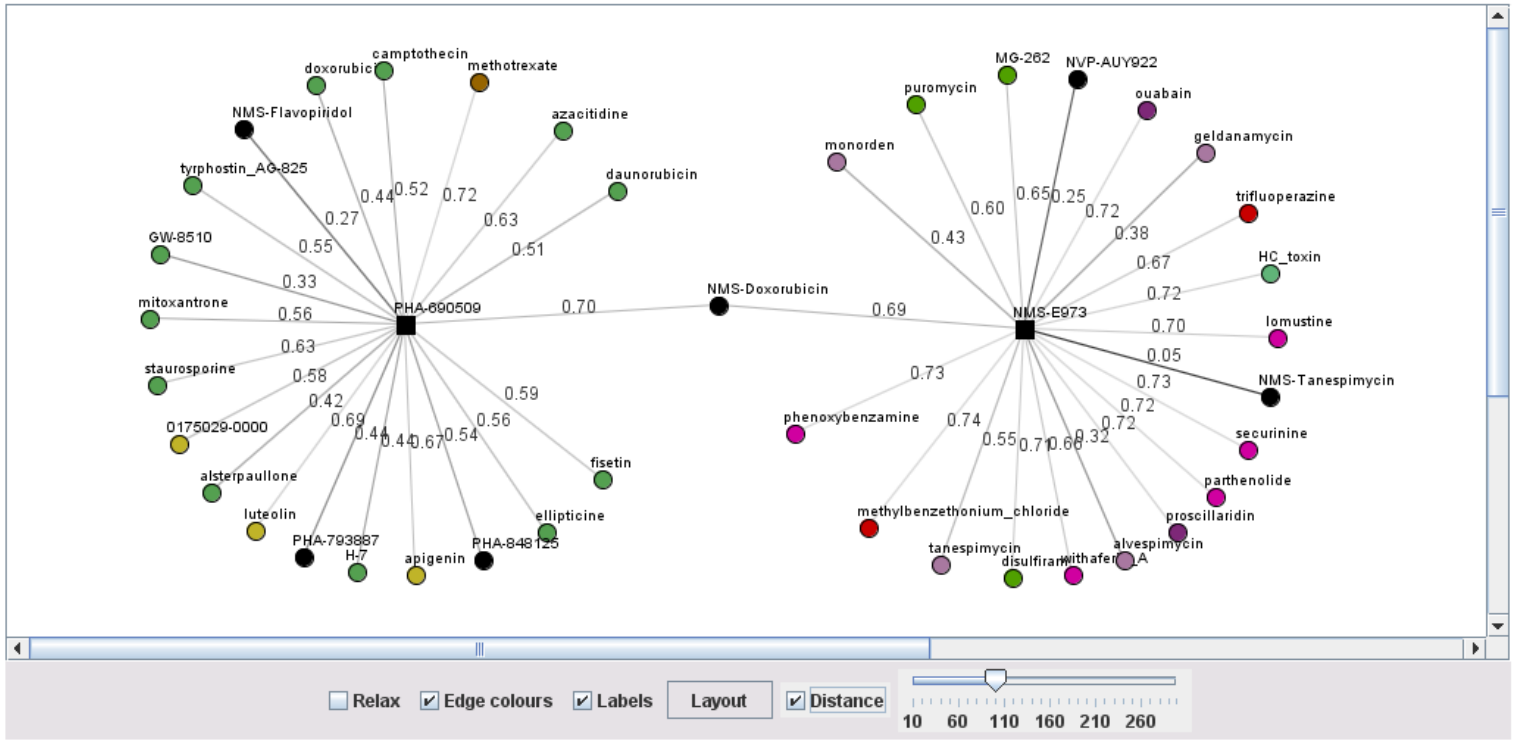
You can unflag "**Labels**" to erase the label of the nodes.

VIEW - Applet Menu: Layout



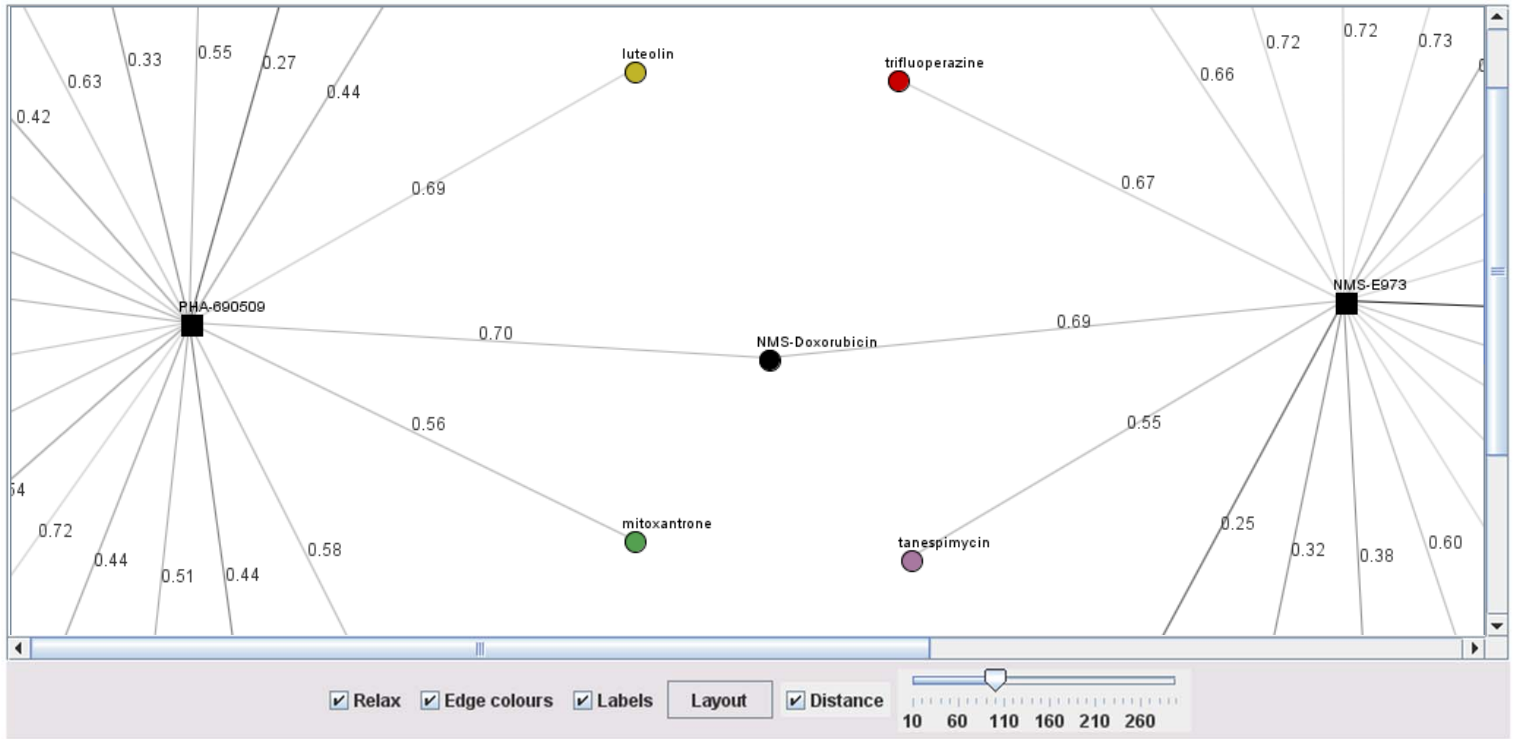
You can click on "**Layout**" to change the network topology.

VIEW - Applet Menu: Relax



You can flag "**Relax**" to relax the network edges.

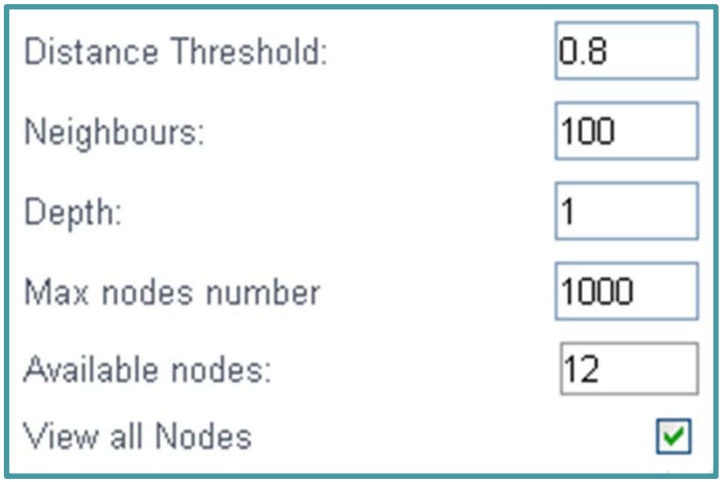
VIEW - Applet Menu: Zoom



You can move the **sliding bar** to zoom in a part of the network.

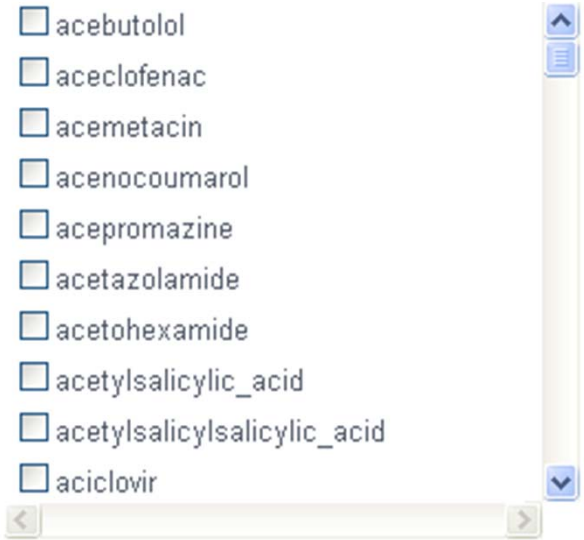
VIEW - Navigation Menu

From the left side menu you can edit the search parameters to browse the network



- Threshold to filter the network based on the edges distance
- Number of nodes by visualize near at the selected node
- Level of network navigation
- Max number of nodes visualizable
- Displayed nodes; nodes available on the applet
- Flag to view the entire nodes list or personal nodes only

Available nodes that could be used as targets of network exploration

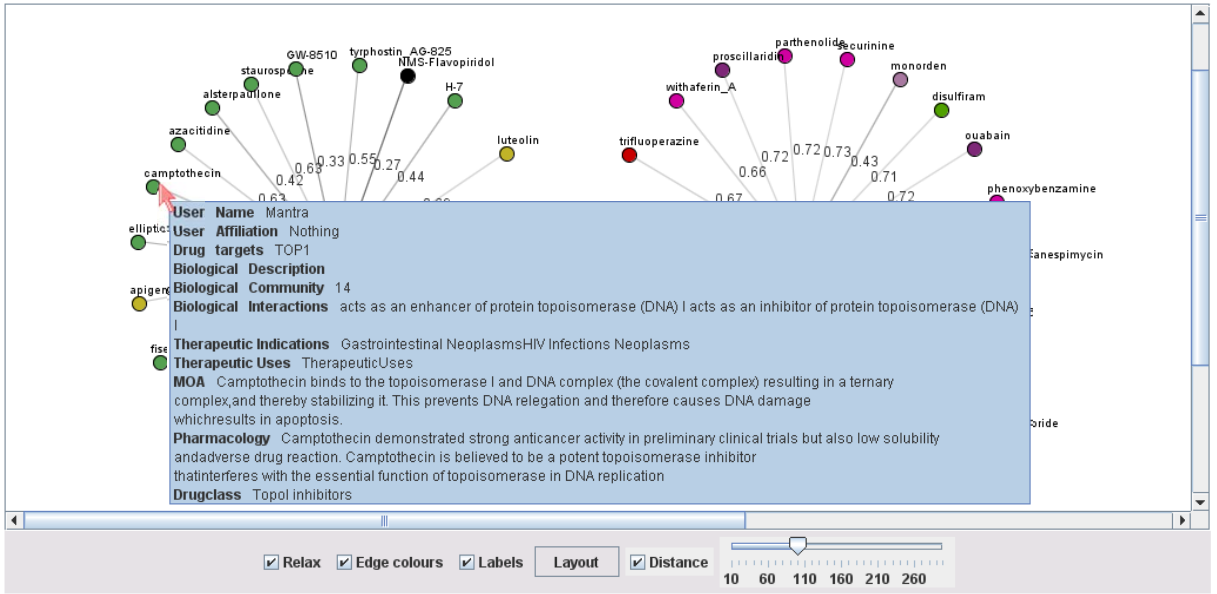


VIEW - Nodes Information

To visualize the nodes information :

1. hover the mouse on a node to open a tooltip

2. press shift + click on node to open an additional information page, with links to external drug databases



idDrugs	1064
DrugName	puromycin
DrugClass	protein synthesis inhibitors (elongation inhibitors)
Community	40
DTargets	
Interactions	
TherapeuticIndications	
TherapeuticUses	
MOA	
Pharmacology	
x	0.5
y	0.5
c	0,255,0
ATC_Code	
IUPAC_Name	3'-{[(2S)-2-azaniumyl-3-(4-methoxyphenyl)propanoyl]amino}-3'-deoxy-N,N-dimethyladenosine
Smiles	COc1ccc(C[C@H]([NH3+])C(=O)N[C@@H]2[C@@H](CO)O[C@H]([C@@H]2O)n2cnc3c(ncnc23)N(C)C)cc1
InChi	InChI=1S/C22H29N7O5/c1-28(2)19-17-20(25-10-24-19)29(11-26-17)22-18(31)16(15(9-30)34-22)27-21(32)14(23)8-12-4-6-13(33-3)7-5-12/h4-7,10-11,14-16,18,22,30-31H,8-9,23H2,1-3H3,(H,27,32)/p+1/t14-,15+,16+,18+,22+/m0/s1
PubChemAccessionNumber	99364948
ChemBankAccessionNumber	-
ChebiAccessionNumber	60255

PubChem CHEMBANK ChEBI

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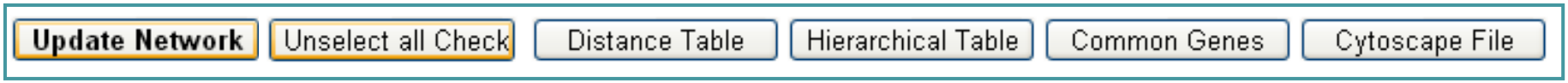
BUTTON PANEL

In the top panel there are six buttons, each with a specific function. The first two buttons can be used to change the displayed network.



Update Network

update the network in basis to selected parameters in the navigation menu and to selected nodes

Unselect all Check

refresh the network unselecting all nodes

BUTTON PANEL - Distance Table

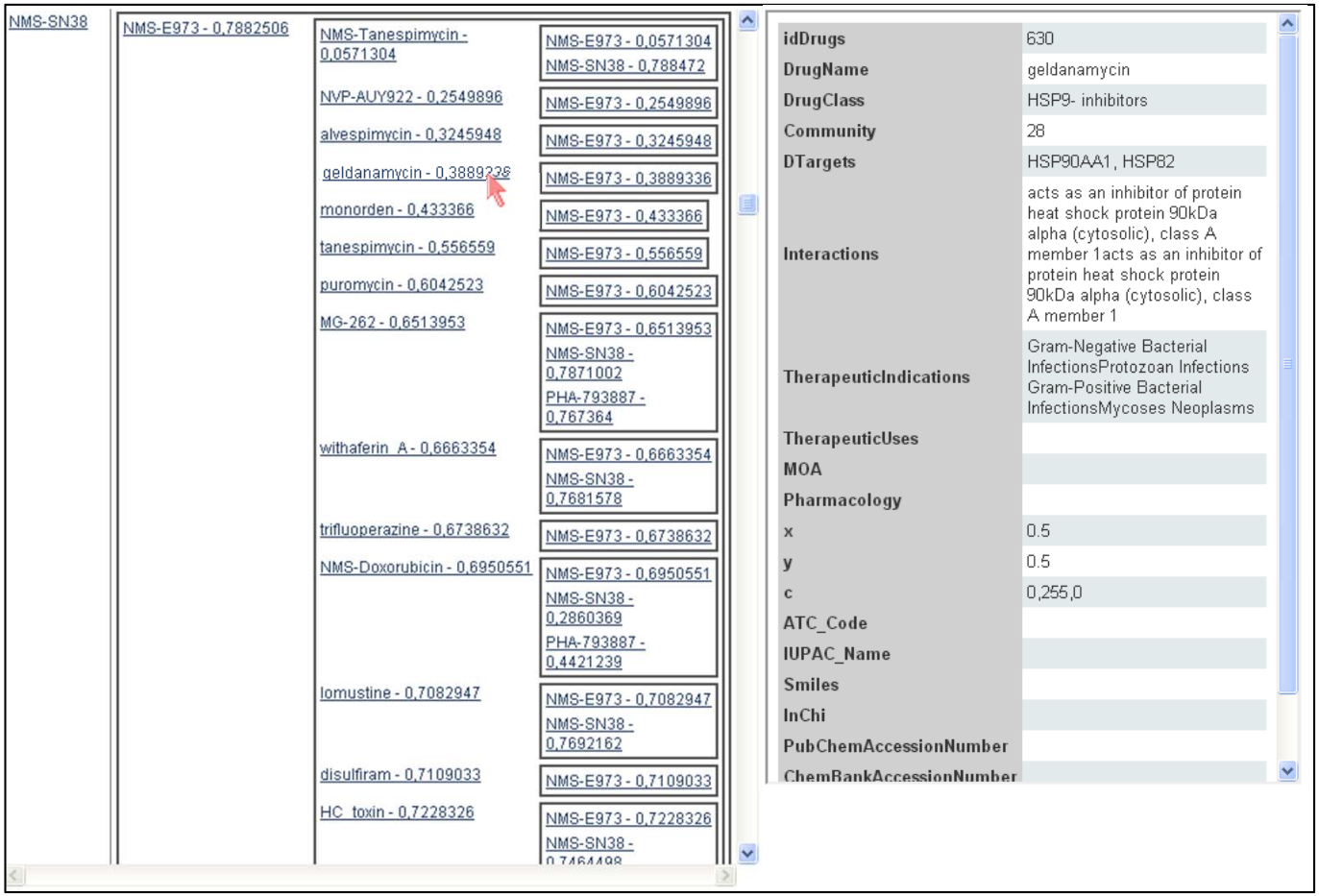
Selected Drug	Distance	Drug2	Community	Description	TherapeuticIndications	Interactions	Drugclass
NMS-E973	0	NMS-E973	0	MCF7 treated E973			
NMS-E973	0,0571304	NMS-Tanespimycin	0	MCF7 treated Tanespimycin-17AAG			
NMS-E973	0,25499	NVP-AUY922	0	MCF7 treated AUY922			
NMS-E973	0,324595	alvespimycin	28				HSP9- inhibitors
NMS-E973	0,388934	geldanamycin	28		Gram-Negative Bacterial InfectionsProtozoan Infections Gram-Positive Bacterial	acts as an inhibitor of protein heat shock protein 90kDa alpha	HSP9- inhibitors
NMS-E973	0,433366	monorden	28			acts as an inhibitor of protein v-src sarcoma (Schmidt-Ruppin A-2) viral	HSP9- inhibitors
NMS-E973	0,556559	tanespimycin	28				HSP9- inhibitors
NMS-E973	0,604252	puromycin	40				protein synthesis inhibitors (elongation
NMS-E973	0,651395	MG-262	40				Proteasome inhibitors and UPS
NMS-E973	0,666335	withaferin_A	104				-
NMS-E973	0,673863	trifluoperazine	100		Vomiting	acts as an antagonist of protein dopamine receptor D2	Antipsychotics (Phenothiazines)
NMS-E973	0,695055	NMS-Doxorubicin	0	MCF7 treated Doxorubicin			
NMS-E973	0,708295	lomustine	104				nitrosourea compounds used as

This table contains the distances of displayed edges and the details of nodes near to selected nodes (such as Community, Description, Therapeutic Indications, Interactions, Drug Class, etc.).

BUTTON PANEL - Hierarchical Table

This table contains a hierarchical structure in basis to the connections.

Clicking on a name you can visualize the node information in a right window.



BUTTON PANEL - *Common Genes*

This button generates a dialog with the analysis of common genes between selected nodes.

In particular, you will have two **On/Off** tables:

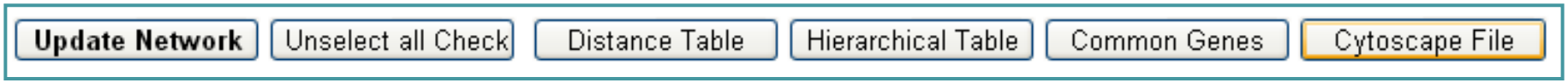
1. Down Regulated genes
2. Up Regulated genes

Down Reguleted common genes - On/Off Table

Gene	PHA-793887	NMS-E973	NMS-SN38
ARMC8 - 219094_at	X	O	X
ATAD2B - 213387_at	X	O	X
BUB1B - 203755_at	X	O	X
C9orf91 - 221865_at	X	X	O
CCNE2 - 211814_s_at	X	X	O
CEBPB - 212501_at	X	X	O
CENPA - 204962_s_at	X	O	X
CENPE - 205046_at	X	O	X
CHAC1 - 219270_at	X	X	O
EML1 - 204796_at	X	O	X
ID4 - 209291_at	X	X	O
INHBE - 210587_at	X	X	X
JMJD4 - 218560_s_at	X	X	O
KIF11 - 204444_at	X	O	X
KIF18A - 221258_s_at	X	O	X
MEIS1 - 204069_at	X	O	X
METTL1 - 204027_s_at	X	X	O
NDC80 - 204162_at	X	O	X
PAFAH1B1 - 211547_s_at	X	O	X
PDS5B - 204742_s_at	X	O	X
PLK1 - 202240_at	X	O	X
PRIM1 - 205053_at	X	X	O
PSRC1 - 201896_s_at	X	O	X
RASAL2 - 219026_s_at	X	O	X
RBL1 - 205296_at	X	O	X
SAP30 - 204900_x_at	X	O	X
SR140 - 212061_at	X	O	X
SRSF3 - 208673_s_at	X	O	X
TBC1D30 - 213913_s_at	X	O	X
TRIB1 - 202241_at	X	X	O
TRMT61B - 221229_s_at	X	X	X
TSEN2 - 219581_at	X	X	O
VAV3 - 218807_at	X	O	X
VLDLR - 209822_s_at	X	O	X
CYP24A1 - 206504_at	O	X	X
GMPS - 214431_at	O	X	X
MAP3K5 - 203837_at	O	X	X
MSH2 - 209421_at	O	X	X
TP63 - 209863_s_at	O	X	X

BUTTON PANEL - Cytoscape File

Cytoscape is an open source bioinformatics software for visualization and analysis of interactions networks.

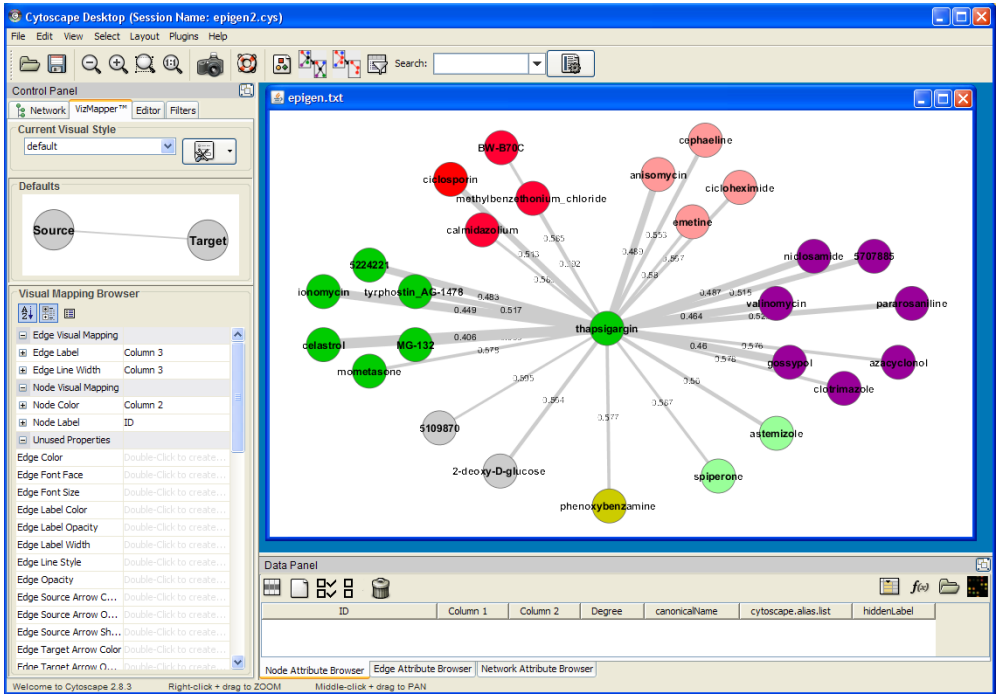


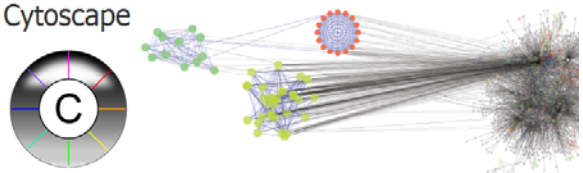
Creates a **SIF** (Simple Interaction Format) file: a text format invented for Cytoscape. It consists of 3 columns: source, interaction type (distance), and target.

```
nodeA <relationship type> nodeB
nodeC <relationship type> nodeA
nodeD <relationship type> nodeE
```

In Cytoscape:

File → Import → Network (Multiple File Types)





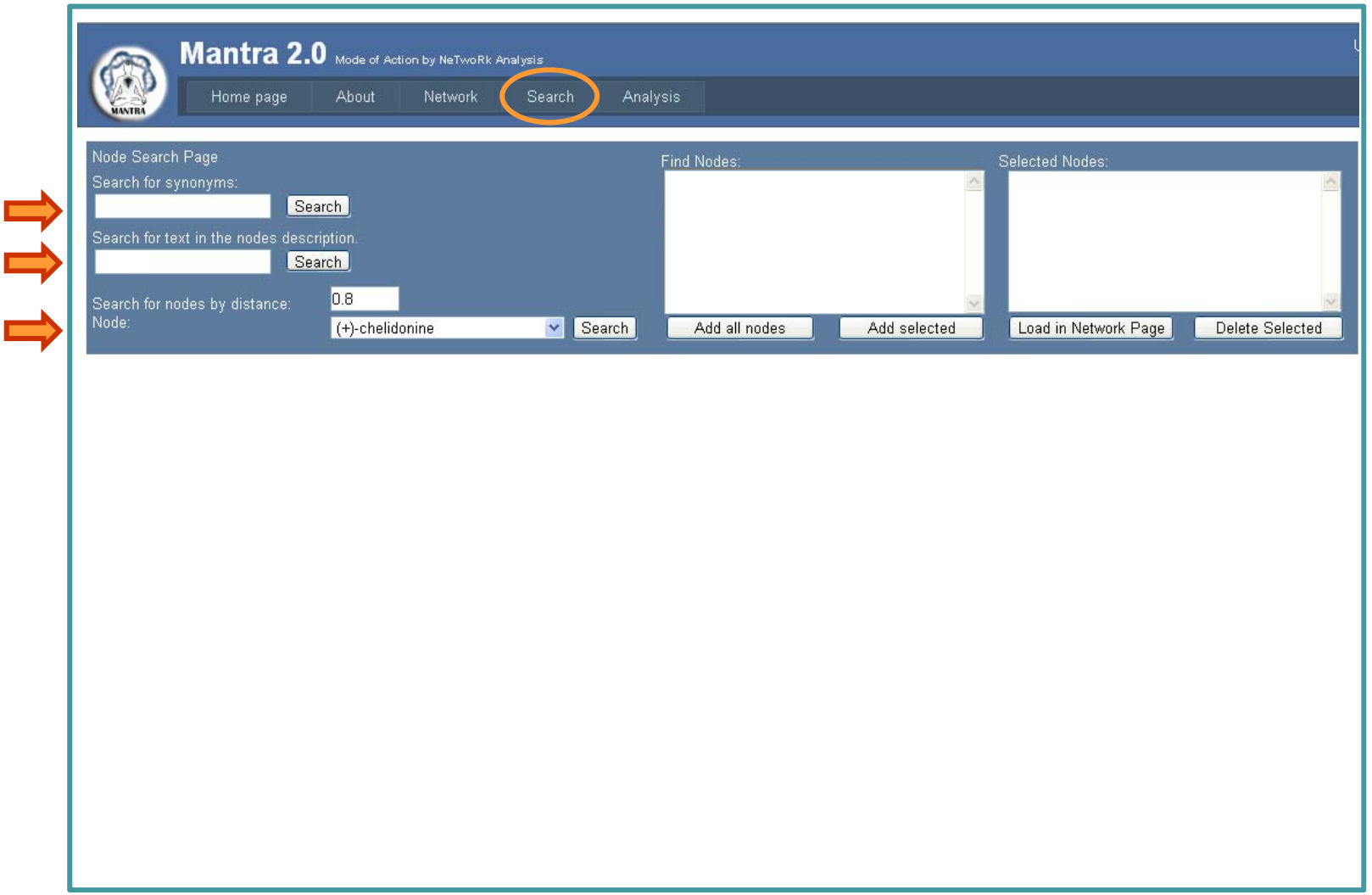
http://www.cytoscape.org/

OUTLINE

1. MANTRA Web Tool
2. Analysis
   a) New Experiment
   b) New Node
   c) GSEA
3. Network
   a) View
   b) Button Panel
4. Search
5. In Summary
6. Conclusion

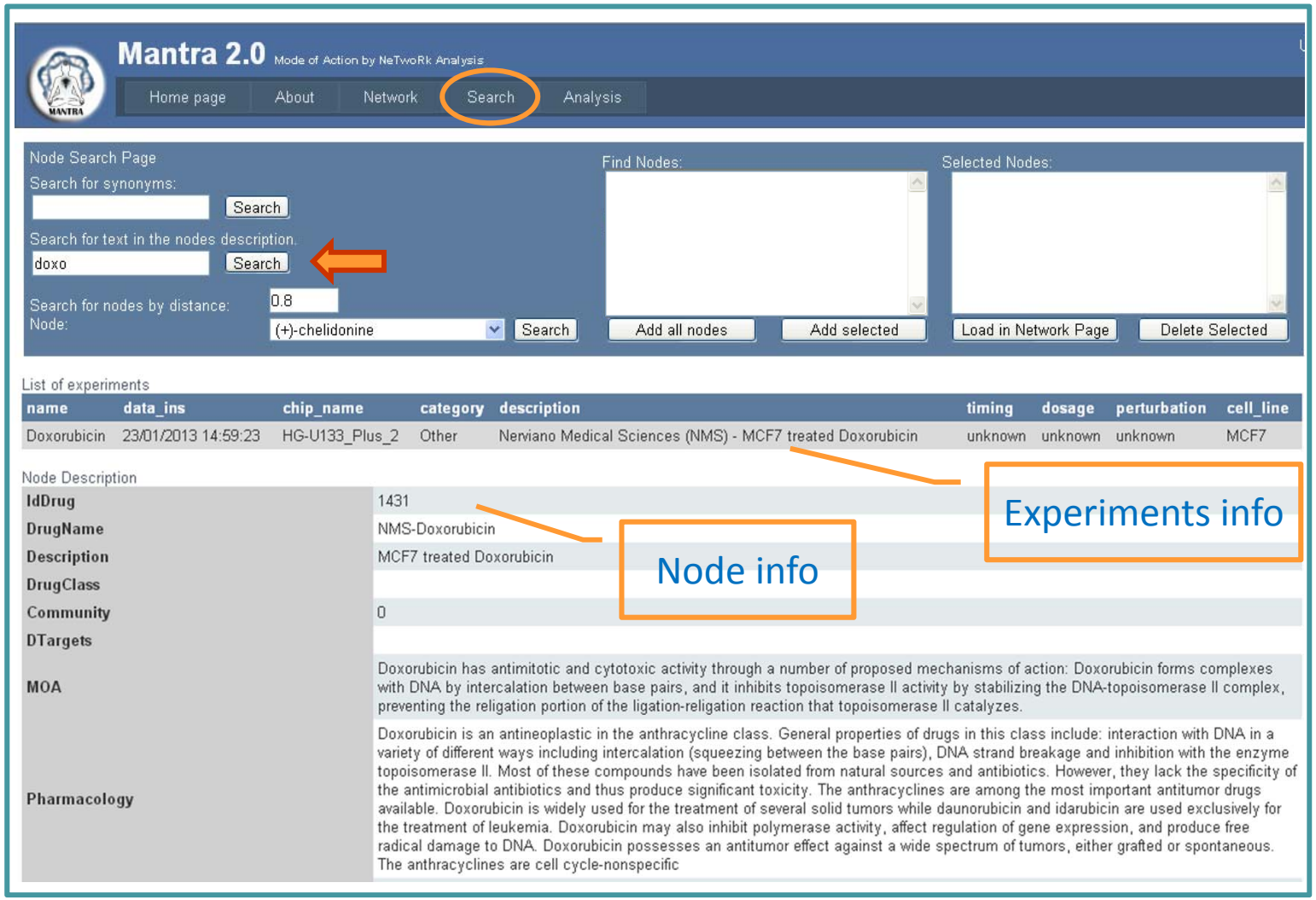
SEARCH

The Search tab provides three different search mode: "**Search for synonyms**", "**Search for text in the nodes description**", "**Search for nodes by distance starting one node**".



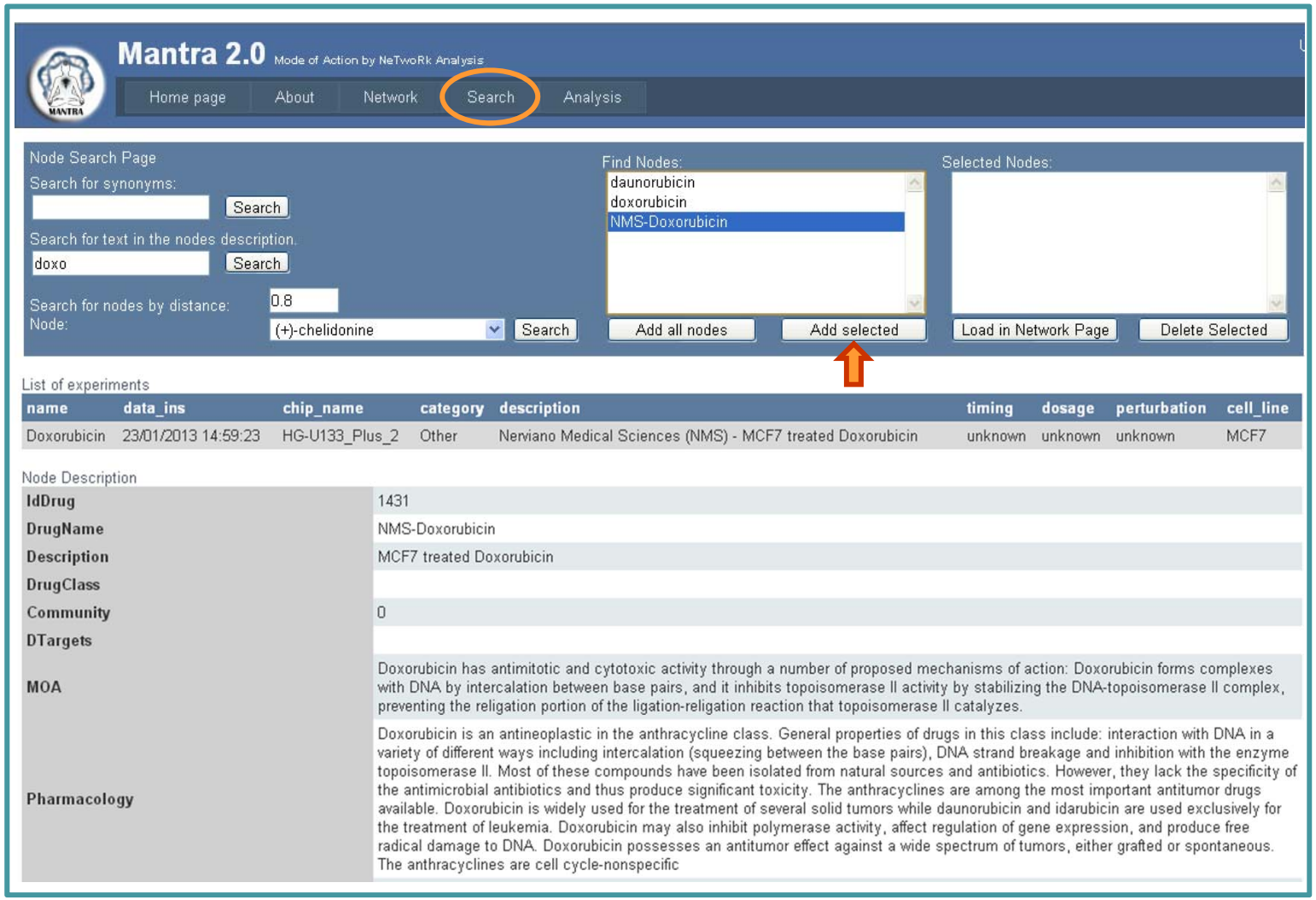
SEARCH

Selecting one node from the search results, it is possible to display the node description and experiments detail.



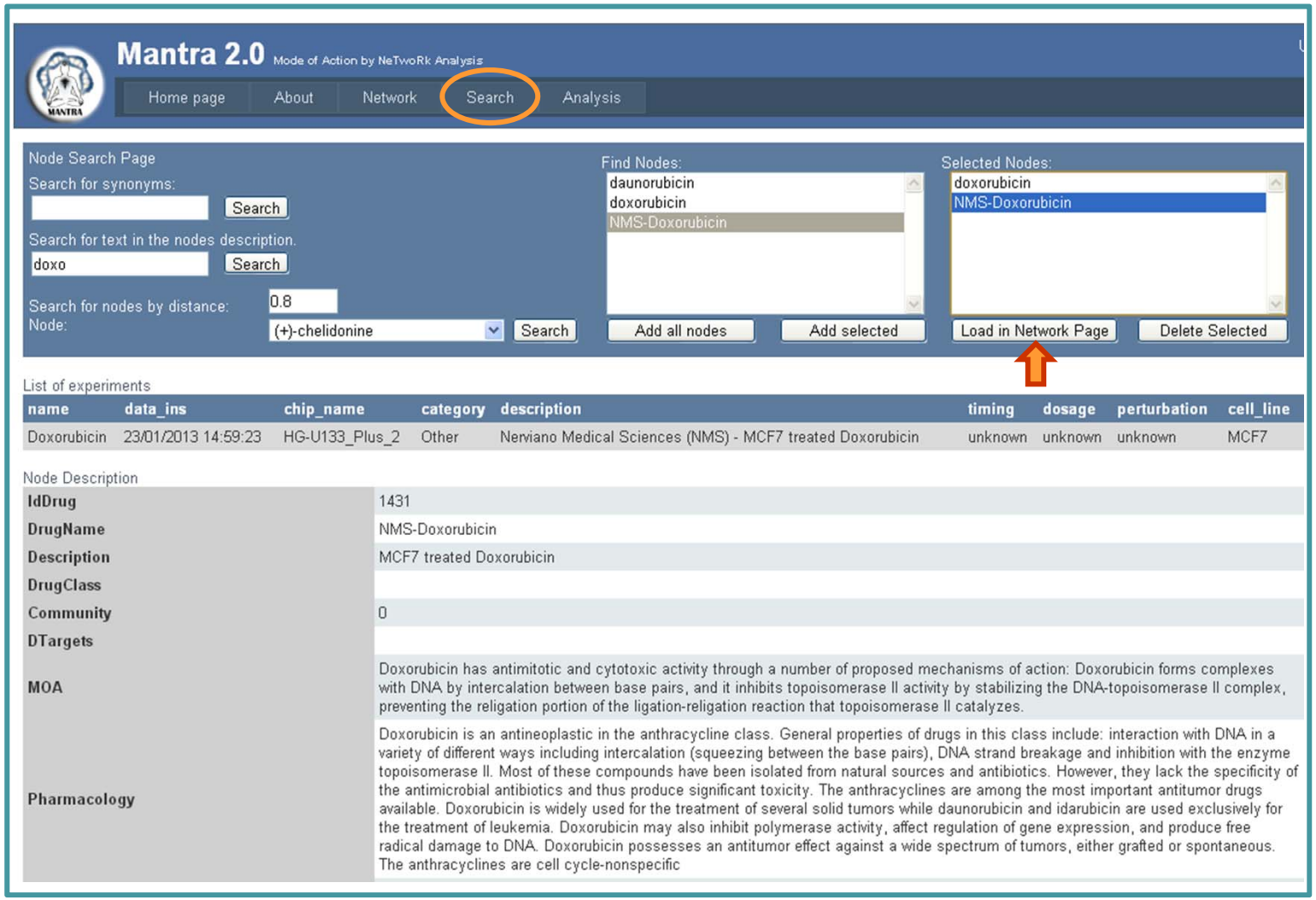
SEARCH

The search results can be added, all or individually, at the "**Selected Nodes**" box.



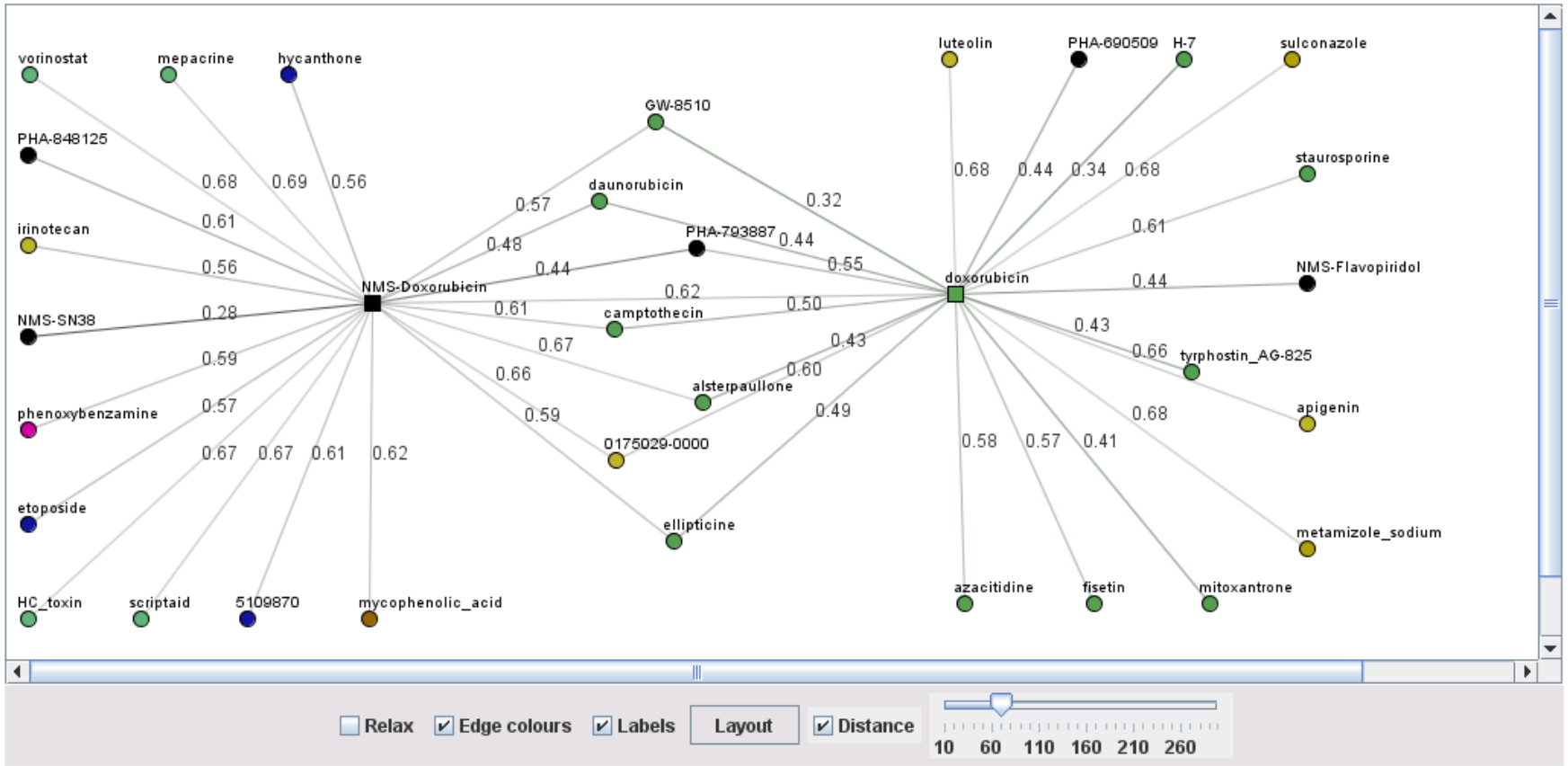
SEARCH

The selected nodes can be loaded directly in Network Page clicking on "**Load in Network Page**" button.



SEARCH

The search results can be selected and loaded directly in Network Page.



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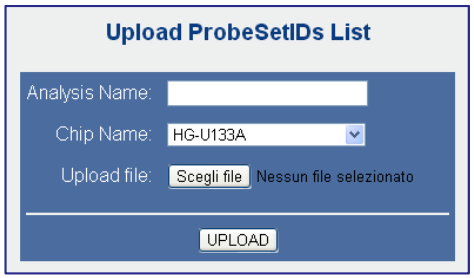
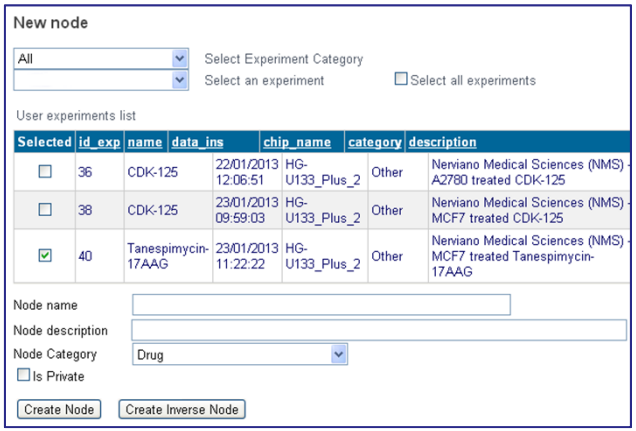
IN SUMMARY - Workflow

Input

Step 1: Uploads the Experiments

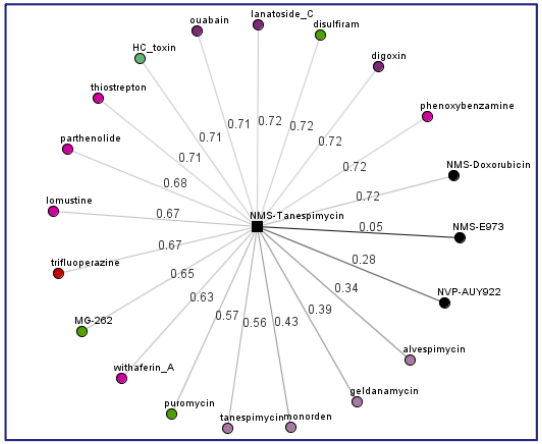


Step 2: Create New Nodes



Output

Network View



0.0 Distance 1.4

Tabulated Results

Selected Drug	Distance	Drug2	Community	TherapeuticIndications
NMS-Tanespimycin	0.391792	geldanamycin	28	Gram-Negative Bacterial InfectionsProtozoan In Gram-Positive Bacterial InfectionsMycoses Ne
NMS-Tanespimycin	0.431153	monorden	28	
NMS-Tanespimycin	0.673294	trifluoperazine	100	Vomiting
NMS-Tanespimycin	0.675602	lomustine	104	
NMS-Tanespimycin	0.685952	parthenolide	104	Neoplasms Bacterial Infections

In step 1, the user uploads the experiments data in affymetrix-compatible format. **In step 2**, the user can filter the experiments based on the characteristics and annotation, and create new nodes. After processing, the recalculated network is available in a viewer of web-based interactive and in several tabulated formats (as a Distance Table, a Cytoscape-compatible format, and browser tables with links to external source databases).

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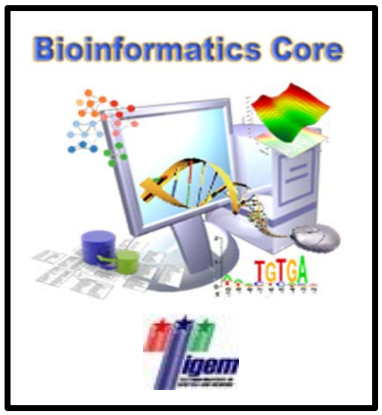
CONCLUSION

- The potential of the massive quantity of public available gene expression data has not been fully exploited.
- A significant number of published works showed that it is possible to identify drug repositioning opportunities by using genome-wide signature-matching methods.
- MANTRA web tool is the construction of unique platform in which it is possible to explore and expand the network of drugs. In addition to hypothesize new therapeutic applications for approved drugs, already present in the network, it is possible to study the repositioning of new drugs by analyzing their neighbors.

Thanks !


igem
TELETHON INSTITUTE OF GENETICS AND MEDICINE
di Bernardo Lab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