

GFD-NET



Cytoscape Plug-in

GFD-Net is a Cytoscape app designed to visualize and analyze the functional dissimilarity of gene networks. GFD-Net can analyze a gene network based on Gene Ontology (GO) and calculate a quantitative measure of its functional dissimilarity, i.e. a quantitative value of the degree of dissimilarity between the connected genes in it. After the analysis, users can visualize the information retrieved from GO. For each gene the user can see its associated GO terms and its function (specified by a GO term) chosen as the most cohesive function in the set. For each edge the user can see the genes at it sends, the function chosen as the most cohesive function in the set for each one and the dissimilarity between them.

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Introduction

This manual aims to provide basic knowledge for any user, regardless of their computer skills, to be able to use the GFD-Net app for Cytoscape.

GFD-Net is a Cytoscape app that allows the user to analyze genetic networks. GFD-Net analyzes the networks based on Gene Ontology, calculates a quantitative measure of its consistency and provides additional information about the genes that form it and the interactions between them.

What is it for?

GFD-Net provides a new approach to assessing the functional dissimilarity of a gene network, i.e. the degree of dissimilarity between genes forming it considering the relationships the network defines between them. This will reveal the quality or reliability of a network obtained from an experiment and see in which sense or with which function the genes are more consistent with each other since a gene may have more than one function in the body.

Consistency is measured from a repository of "real" biological information as the Gene Ontology (GO), which provides a controlled vocabulary that describes the gene and gene product attributes in any organism. Each gene is associated with multiple GO terms, and through them it is possible to compare the functional similarity.

It is important to note that GFD-Net is designed to analyze completely connected networks where all its genes are annotated in GO.

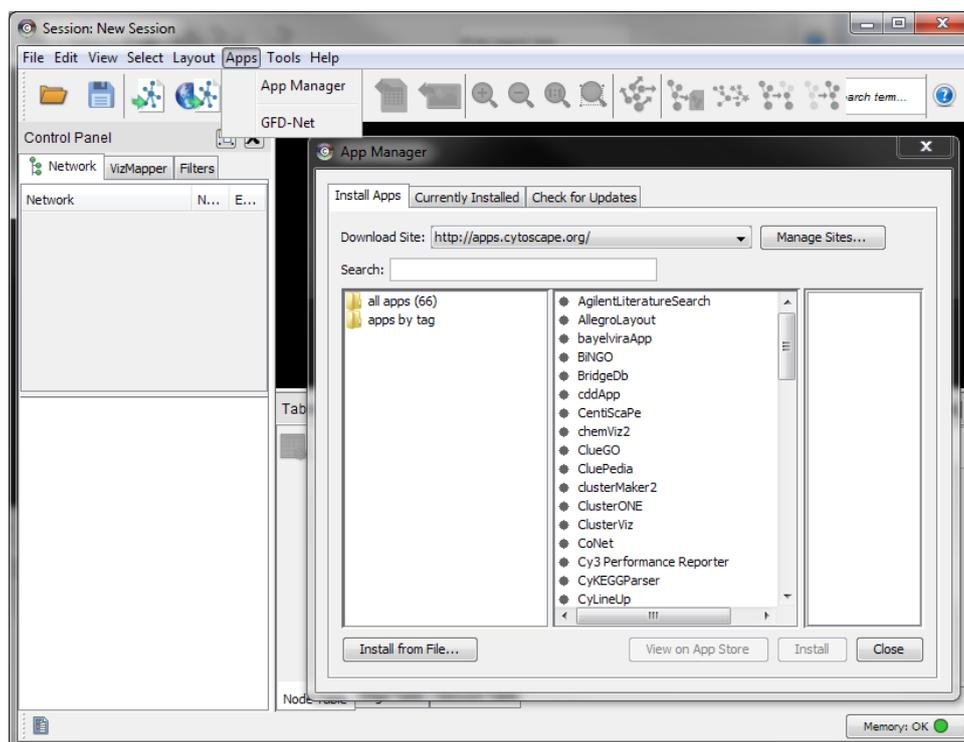
More information and use cases can be found at <http://f1000research.com/articles/3-142>

Requirements and installation

Requirements

GFD-Net only required a suitable version of Cytoscape (<http://www.cytoscape.org>) in order to work. GFD-Net app needs Cytoscape 3.0 or higher to work but we also offer a plugin that works for all the 2.X versions.

Installing the GFD-Net



Installing through the Cytoscape App Manager

Click on Apps > App Manager. The manager is displayed showing all the installed apps and all the available apps. Search for GFD-Net, select it and click on the Install button to install it.

Installing through the Cytoscape App Store

Go the app store, <http://apps.cytoscape.org/apps/gfdnet>. If you have a valid version of Cytoscape installed, a "Install" or "Upgrade" button will show for installing or upgrading the app in you Cytoscape

Installing from jar file

Click on Apps > App Manager. Click on the "Install from File..." button at the bottom left. Select the file jar of GFD-Net file (can be downloaded from <http://juanjodiaz.github.io/gfdnet/>) and it will be installed.

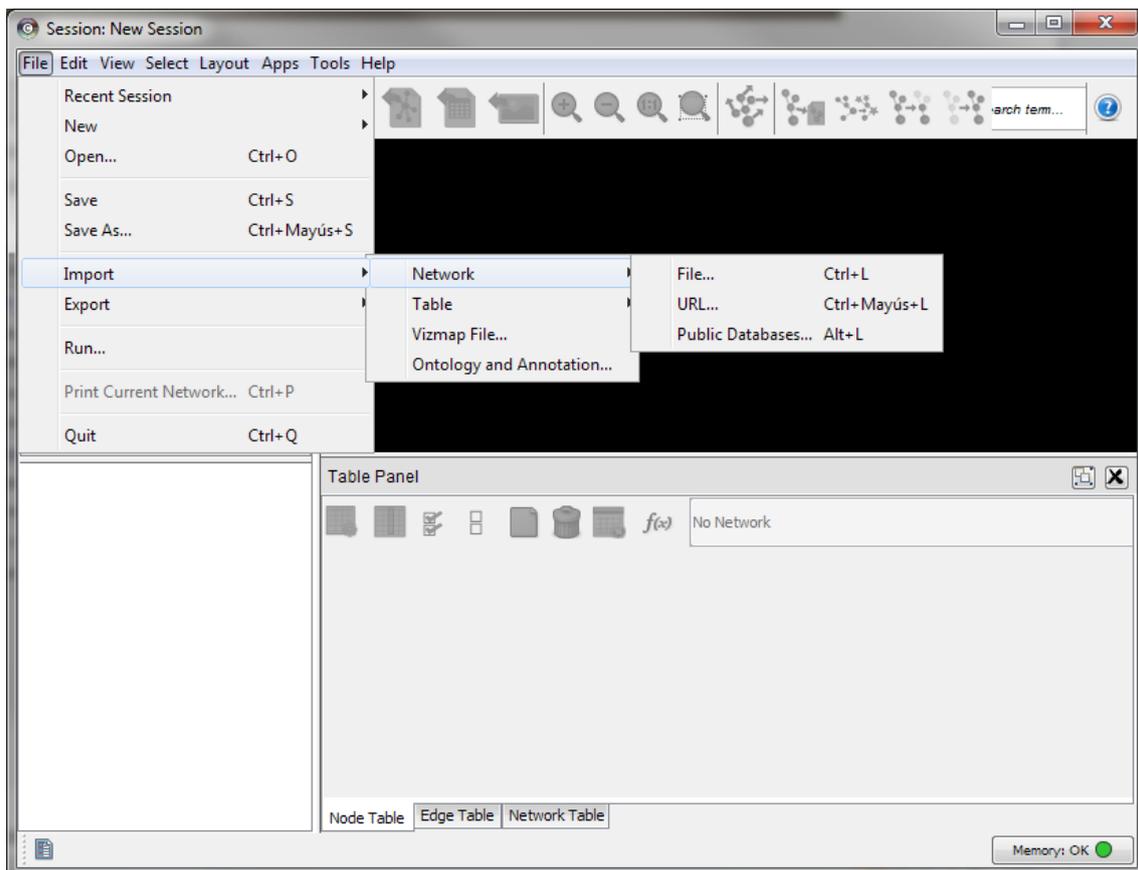
Uninstalling

Click on Apps > App Manager. Go to the "Currently Installed" tab, select Gfd-Net and click on the "Uninstall" button at the bottom to uninstall it.

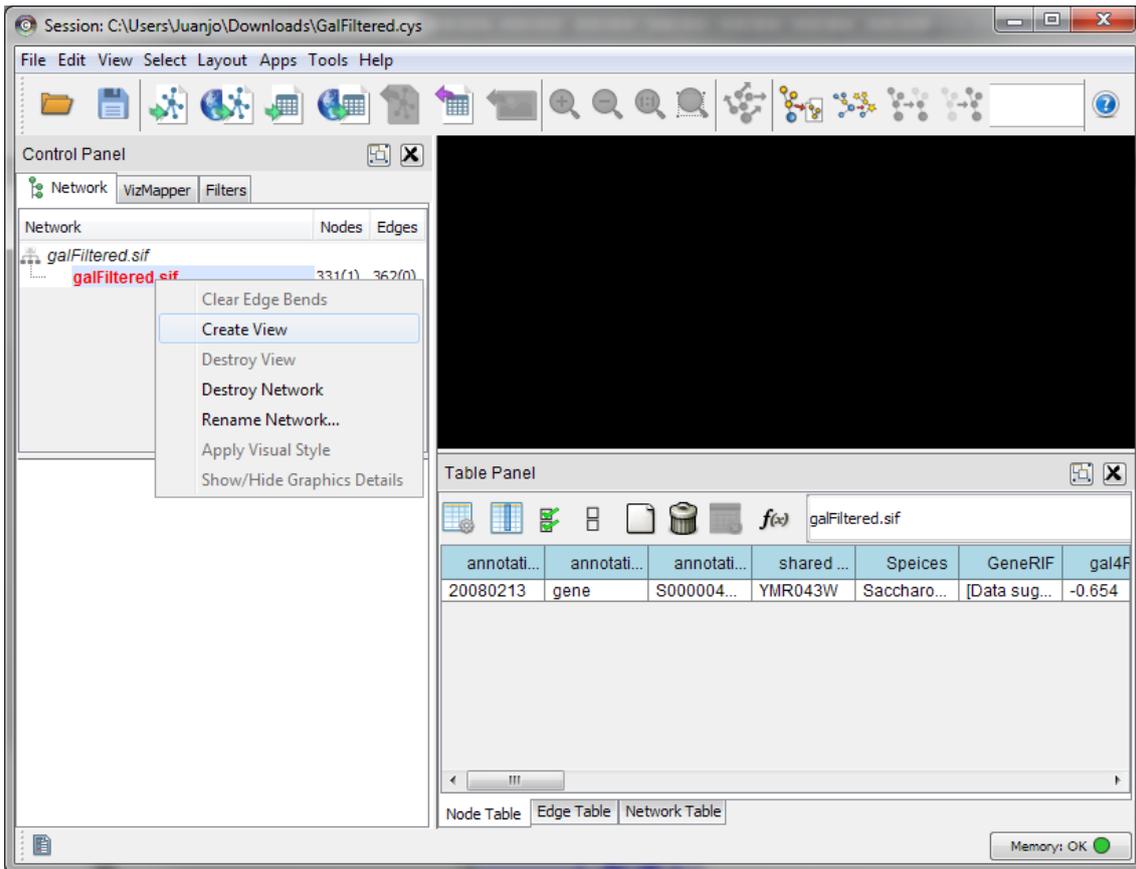
Use of GFD-Net

Launch the plug-in

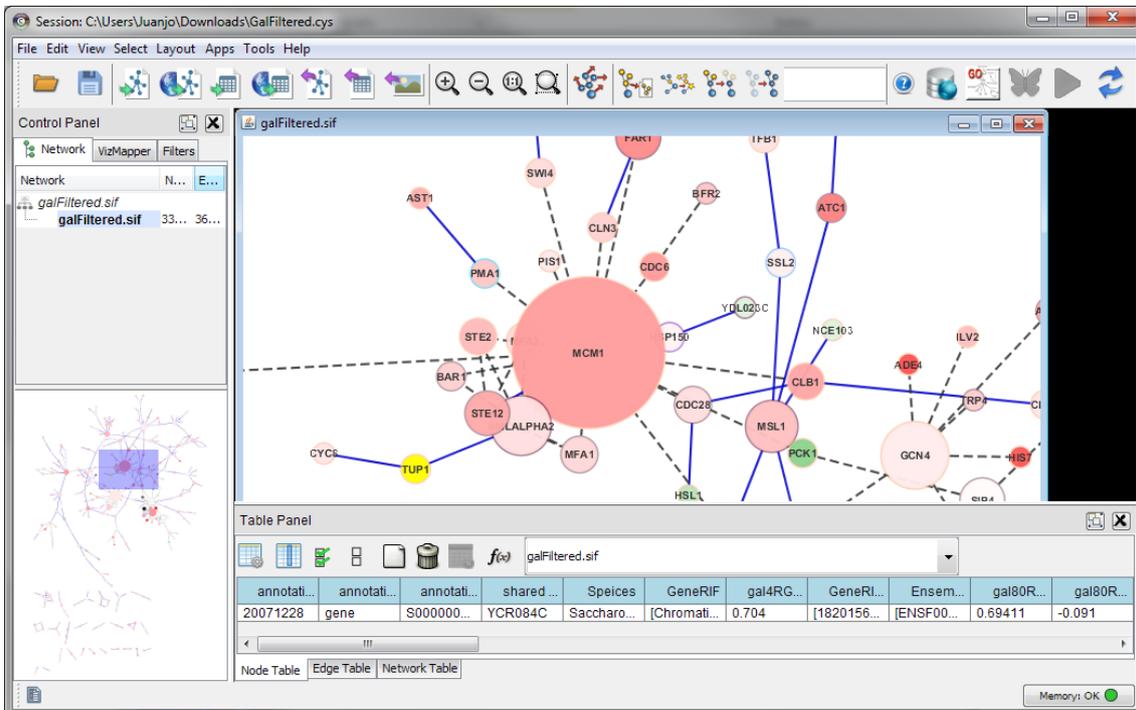
To launch GFD-Net you must load a network view in Cytoscape. This can be done from the menu **File > Open** or **File > Import > Network > ...**



It must be taken into consideration that Cytoscape only creates a network view if you have less than 10000 nodes. If the network is greater, it must be created manually. This can be done by clicking the right mouse button on the network in the control panel to the left and clicking "Create View".



After correctly loading the network and its view, launch the plugin from the menu Apps > GFD-Net. The GFD-Net buttons are then added to the toolbar but only "Configure DB Connection", "Set Ontology" and "Refresh" can be used.



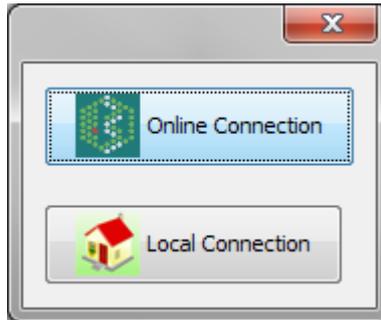
If you try to launch GFD-Net without having a network view selected the message "A valid network view should be loaded." will be display and GFD-Net will not be launch.

Configuration

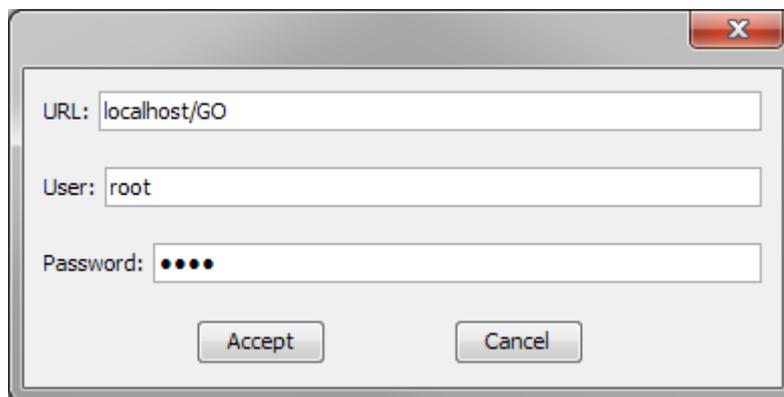
The first thing to do in order to run a GFD-Net analysis is to configure their parameters correctly. For this purpose the best way is to use the following steps.

Configure the BD

To set the connection to the database, click the  button. A dialog is displayed giving the user the option to connect to the online GO database provided online by the European Bioinformatics Institute (<http://www.ebi.ac.uk>) or to a local database (or not necessarily local; any address can be accessed). It is advised to use a local database if you intend to run GFD-Net intensively.



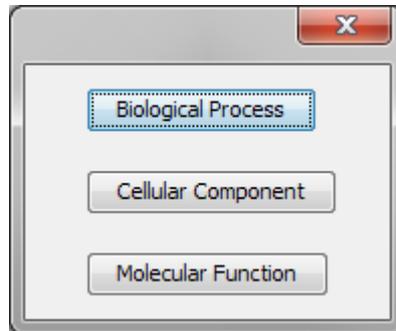
When choosing to use a local database, a form is displayed asking for the database address, user and password. This allows you to not only access databases in our local system but also in any other accessible address.

A dialog box with a close button (X) in the top right corner. It contains three input fields: "URL:" with the text "localhost/GO", "User:" with the text "root", and "Password:" with five black dots. At the bottom, there are two buttons: "Accept" and "Cancel".

Once the database connection is successfully established, the "Set Organism" and "Execute GFD-NET" buttons are enabled.

Set an ontology

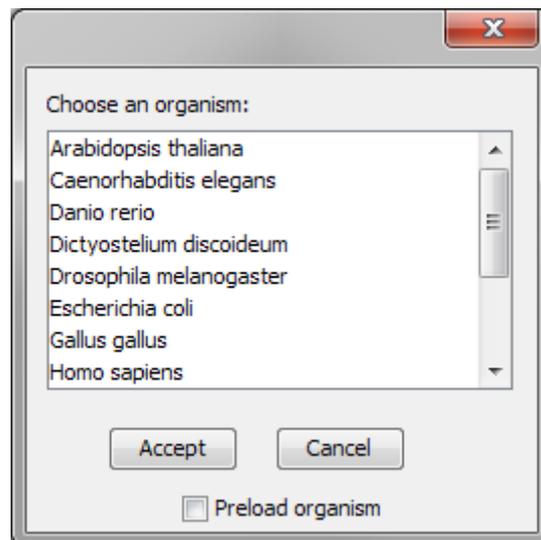
By default, GFD-Net runs on the biological processes ontology, but this can be changed by clicking on  and choosing any other ontology.



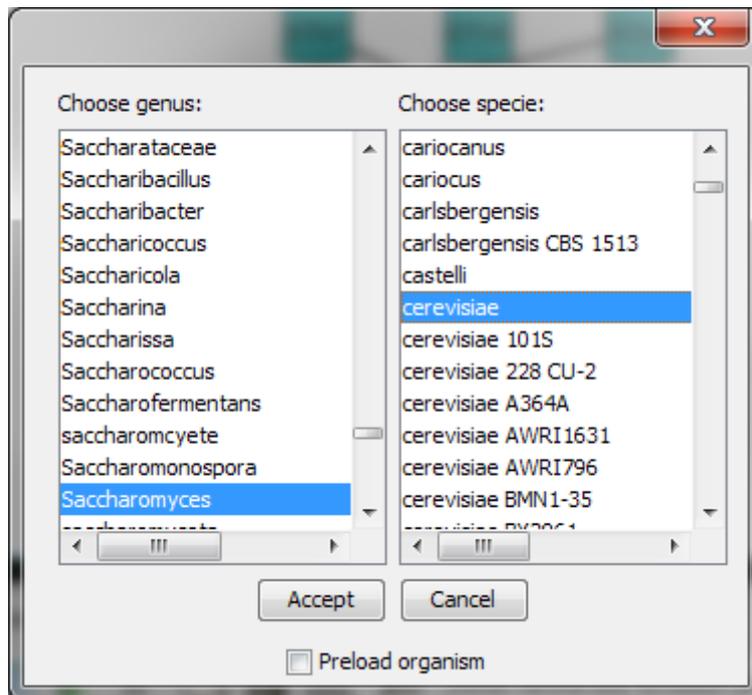
If GFD-Net has already been executed, setting a new ontology would restore the original network and the information obtained in the previous run will be lost.

Set an organism

It is not possible to run a GFD-Net analysis without having an organism set. This can be done by clicking . A dialog is then displayed allowing the choice between the main organisms of GO. In case you want to use another organism, select "Other ...". Select the organism and click "OK" to set it.



If choosing "Other ..." another dialog will be displayed showing a list of the genre contained in the database. Clicking on one of these genres will display a list of species that belong to it. With one genus and one species selected click "OK" to set the organism.



In both cases, there is the option of preloading the organism. Preloading an organism consist on retrieving from the database all the genes and gene products related to it, retrieving all the Go-Term in the selected ontology that annotate it and building the relevant section of the GO-Tree. It makes takes a couple minutes but will save a lot of times if you want to run the analysis on multiple networks belonging to the same organism.

It should be noted that in GO the name of an organism is formed by its genre and specie put together. However, when extracting the genre and specie from the database, the first word is taken as the genre and the rest as specie.

If GFD-Net has already been executed, setting a new ontology would restore the original network and the information obtained in the previous run will be lost.

Refresh

If you want to change the network you are working on simply open a new one and, having the view on the new network as current view, click on . This way the app returns to its initial state but is working on the new network.

Execution:

Execute GFD-Net

To run the analysis, you must set the organism and the ontology as well as the database connection. Clicking on ► start the analysis and show the progress on the Cytoscape interface. The duration of the process depends on the size and complexity of the network introduced and on the amount of information about the organism that is contained in GO.

Once completed, all nodes that were not found in GO are removed from the network, a panel is displayed on the right containing the extracted information and the user is able to interact with the network and the results.

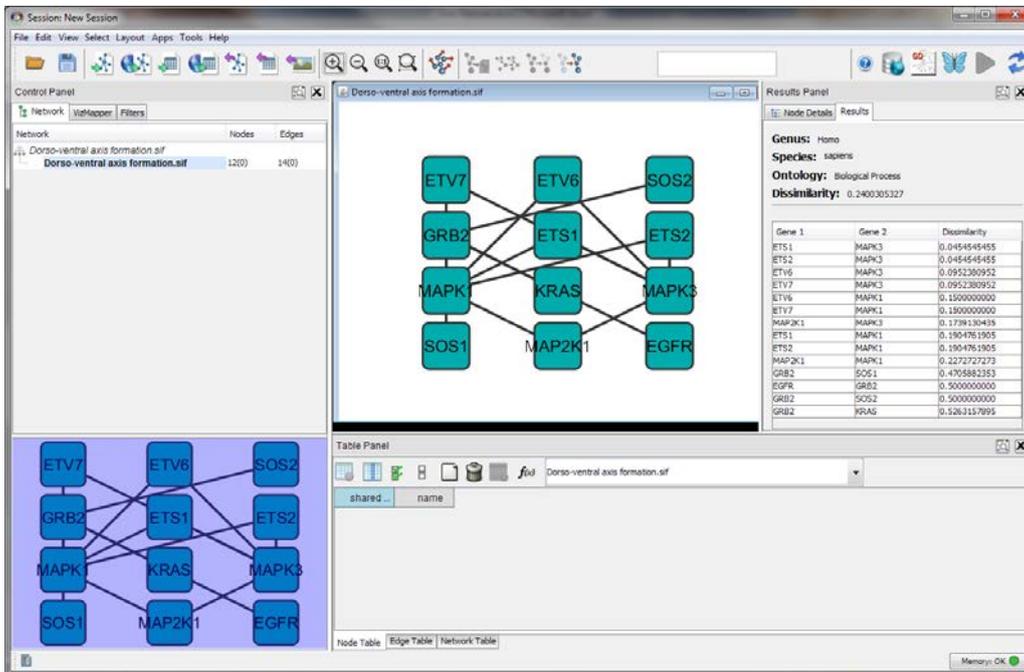
It's important to note that the analysis is CPU intensive so it not advisable to work on the machine that is running the analysis while it is running or run more than one analysis at the same time in the same machine.

To execute GFD-Net in several networks or several ontologies or organisms there are two ways:

- Open the new network and refresh, or choose the new organism or ontology. All the information of the current analysis will be lost and the program will be ready ready to run a new execution. It is important to take in mind that when several networks are loaded at the same time the probability of malfunction of the product is much higher.
- Open a new Cytoscape and make new analysis there. As it is possible to open as many instances of Cytoscape as wanted, it is possible to have many executions at the same time and see the result of all of them just changing the window.

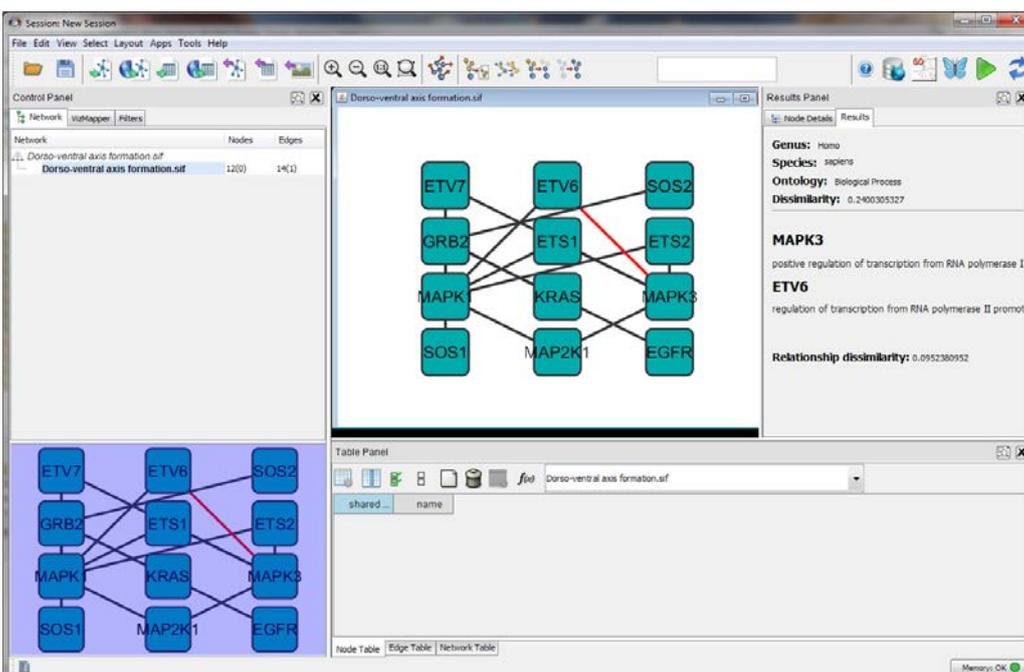
Information Visualization

Once GFD-Net is executed, a panel is displayed on the right containing information about the results (ontology, genre, specie and value of dissimilarity of the whole network) and a ranking of the dissimilarity between each pair of nodes. The user can interact with the network in order to visualize the information obtained for each node or edge. Clicking on an interaction in the ranking will show it on the network view and double-clicking will display more info about it.



Interaction (Edge) Information

Clicking on an edge will show the names of the genes located at its ends, the representation chosen for each of them and the dissimilarity value between them. Double-clicking on the name of a node will display the information obtained about it.



Gene (Node) Information

Clicking on a node adds information about it to the panel on the right, including its name and a list of its related GO-terms. The first GO-terms of the list will be shaded indicating that is the function chosen by GFD-Net as the most cohesive for the network.

The screenshot displays the GFD-Net software interface. The main window is titled "Session: New Session" and contains several panels:

- Control Panel:** Shows a network list with columns for "Network", "Nodes", and "Edges". The selected network is "Dorso-ventral axis formation.sif" with 12 nodes and 140 edges.
- Network Diagram:** A central panel showing a network of nodes (ETV7, ETV6, SOS2, GRB2, ETS1, ETS2, MAPK, KRAS, MAPK3, SOS1, MAP2K1, EGFR) connected by edges. The node MAPK3 is highlighted in yellow.
- Results Panel:** Displays detailed information for the selected node (MAPK3):
 - Genus: Homo
 - Species: sapiens
 - Ontology: Biological Process
 - Dissimilarity: 0.2400305327A list of GO terms is shown below, with the first term, "GO:0001865 positive regulation of transcription from RNA pol", shaded in light blue.
- Table Panel:** A table with columns "shared" and "name". The first row shows "MAPK3" under "shared" and "MAPK3" under "name".

By double-clicking on one of the representations in the list, the browser will display the website for that GO term in AmiGO, a Gene Ontology online browser.

Advanced User

For advanced users who want to use GFD-Net differently or independently of Cytoscape, it can be done using the existing API. Unfortunately, this API has not been released yet. Release date is pending.

Troubleshooting

Below is a list of common user mistakes when using the app as well as tips on how to avoid them.

- *Error when installing “Unsupported major.minor version XX.0” is produced because you are running Cytoscape with an inappropriate version of Java. Try getting the last one.*
- *Error when launching the app “A valid network view should be loaded.” Is produce because no network view is opened and selected.*
- *Opening a new session keeps the app loaded but eliminates the network. It should be loaded again, and the app must be refreshed to continue using it.*
- *Saving the session does not save the state of the app or information obtained by it.*
- *Changing the network without refreshing causes malfunctions on the app.*