

# Interference

## A tool for virtual experimental network topological analysis

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### A Cytoscape plug-in for virtual knock-out experiments on complex networks!

Centrality indexes allow categorizing nodes in complex networks according to their topological relevance (see [CentiScaPe plugin](#)). In a node-oriented perspective, centralities are very useful topological parameters to compute in order to quantify the effect of individual node(s) alteration. We have introduced the notion of interference and developed the Cytoscape plugin **Interference** to evaluate the topological effects of single or multiple nodes removal from a network. In this perspective, interference allows **virtual node knock-out experiments**: it is possible to remove one or more nodes from a network and analyze the consequences on network structure, by looking to the variations of the node centralities values. As the centrality value of a node is strictly dependent on the network structure and on the properties of other nodes in the network, the consequences of a node deletion are well captured by the variation on the centrality values of all the other nodes.

### Potential Applications

The interference approach can model common situations where real nodes are removed or added from/to a physical network:

- **Biological networks**, where one or more nodes (genes, proteins, metabolites) are possibly removed from the network because of gene deletion, pharmacological treatment or protein degradation. Interference can be used to:
  - **Simulate pharmacological treatment**: one can potentially predict side effects of the drug by looking at the topological properties of nodes in a drug-treated network, meaning with that a network in which a drug-targeted node (protein) was removed. To inhibit a protein (for instance a kinases) corresponds to removing the node from the network
  - **Simulate gene deletion**: gene deletion implies losing encoded proteins, thus resulting in the corresponding removal of one or more nodes from a protein network
- **Social and financial networks**, where the structure of the network is naturally modified over time
- **Power grid failures**
- Traffic jam or work in progress in a **road network**
- Temporary closure of an airport in an **airline network**

## How Interference plugin works

The Interference plug-in allows you identifying the area of influence of single nodes or group of nodes. Specifically, Interference:

- Compute the centralities value of the network
- Remove the node(s) of interest
- Recompute the centralities in the new network (the one where the node(s) have been removed)
- Evaluate the differences between the centralities in the two networks.

This allows identifying the differences between the two networks: the one with the node(s) of interest still present and the one where the node(s) have been removed. Some nodes will increase, whereas others will reduce, their individual centrality values. This may suggest hints on the functional, regulatory, relevance of specific node(s).

### Positive Interference

If a node (A), upon removal from the network of a specific node (B) or of a group of nodes, decreases its value for a certain centrality index, its interference value is positive. This means that this node (A), topologically speaking, takes advantage (is positively influenced) by the presence in the network of the node (B) or of that group of nodes. Thus, “removal” of node (B) or of that group of nodes from the network, negatively affects the topological role of the node (A). This is called positive interference.

### Negative Interference

If a node (A), upon removal from the network of a specific node (B) or of a group of nodes, increases its value for a certain centrality index, its interference value is positive. This means that this node (A), topologically speaking, is disadvantaged (is negatively influenced) by the presence in the network of the node (B) or of that group the nodes. Thus, “removal” of node (B) or of that group of nodes from the network, positively affects the topological role of node (A). This is called negative interference.

## Feature List

Interference plug-in computes the Interference values for the following centralities:

- Stress
- Betweenness
- Radiality
- Closeness
- Centroid Value
- Eccentricity

For a formal description of the centralities see the Network Centralities documentation available at:

<http://www.cbmc.it/~scardonig/centiscape/centiscape.php>

For more about interference see the interference tutorial:

<http://www.cbmc.it/~scardonig/interference/InterferenceTutorial.pdf>

## How to do

If you are familiar with the [CentiScaPe plug-in](#) you shouldn't have any problem using the Interference plug-in

- Copy the Interference.jar file to your [Cytoscape\_Home]/plugins directory and start Cytoscape
- Load the network which you want to apply the plugin
- From the Main Menu, Select "Plugins" --> "Interference"

A new panel will appear in the left side of your Cytoscape as shown in figure 1. The panel shows you all the Interference plugin options.

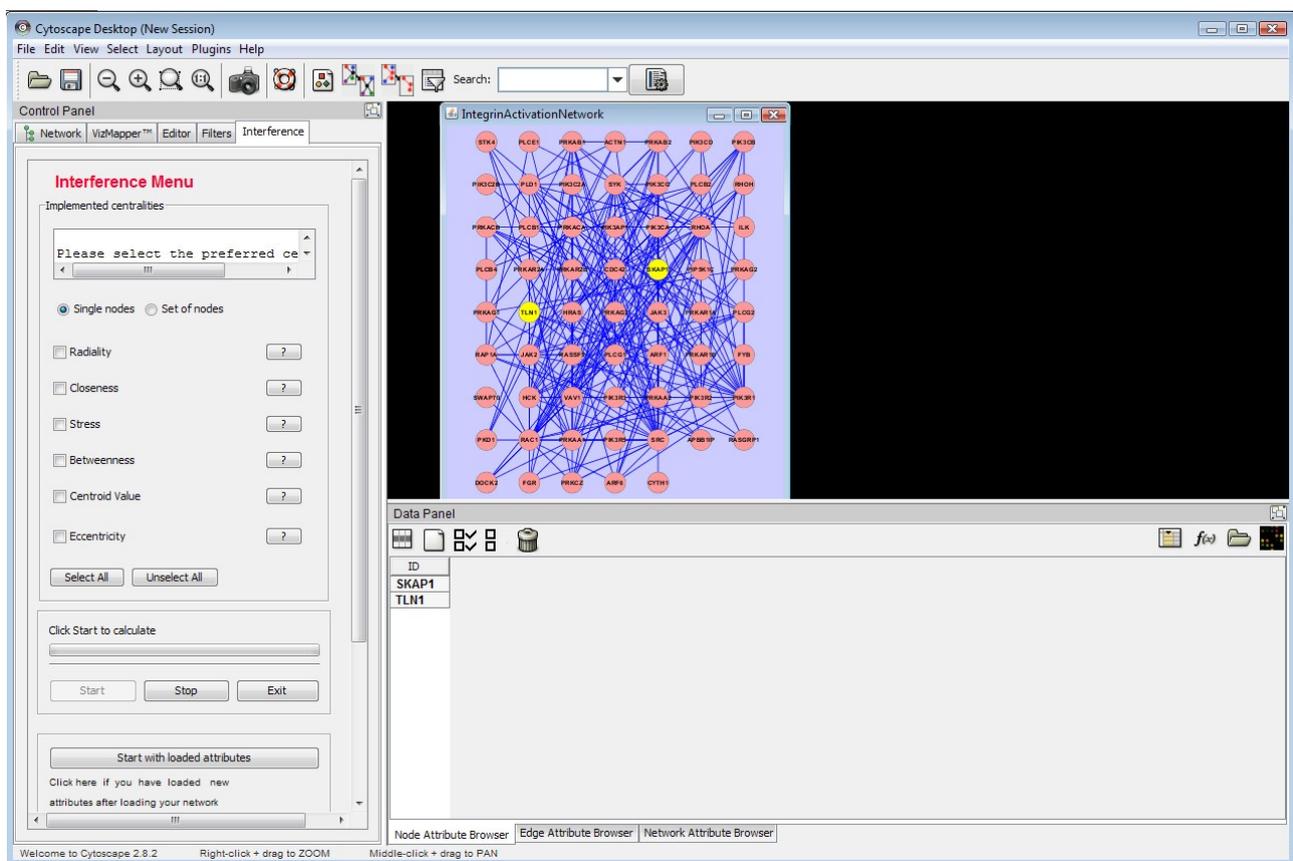


Figure 1:

The steps to use the interference plugin are the following:

1. Select one or more nodes in the network
2. Select the centralities of interest
3. Select the "Single nodes" option (if you want to remove the nodes one by one) or the "Set of nodes" option (if you want to remove all nodes at the same time)
4. Click "Start" and wait for results

## 1. Select one or more nodes in the network

The interference value is computed:

- Calculating the centralities value of the network
- Removing the node(s) of interest
- Recalculating the centralities in the new network (the one where the node(s) have been removed)
- Evaluating the differences between the centralities in the two networks (in percentage with respect to the total value of each centrality).

You have to select the node or the nodes you want to remove from the network. The output will be the interference values of these nodes with respect to the overall network. This allow you to evaluate the effects of these nodes adding or deletion to/from the network and to find which are the area of major influence of these nodes.

## 2. Select the centralities of interest

Interference is a centrality-based notion evaluating the effect of nodes deletion in a network through the variation in the centralities values. The meaning of the interference strictly depend on the meaning of the centralities selected to evaluate such a variation. You can compute the Interference value for the following centralities:

- Eccentricity
- Closeness
- Betweenness
- Stress
- Centroid
- Radiality

On the right side of each centrality button there is also an help button. If you click on it a brief description of the centrality and of the Interference meaning will appear.

## 3. Select the “Single nodes” or the “Set of nodes”

If you have selected more than one node, you can have two option:

- **Single nodes:** this remove the nodes one by one. It means that the first node is remove and then interference is computed. After the computation the node is re-added to the network and the computation restart removing the second node. This process is repeated for all the nodes you selected. You will have one computation and one final result for each selected node. The results are the interference values of all the single nodes with respect

to the overall network. In a protein network this correspond to inhibit one proteins at a time in the virtual experiment.

- **Set of nodes:** This remove all the selected nodes at the same time (as a unique meta-node). It means that all the nodes are removed from the network and the interference is computed. You will have only one computation and only one result (for each centrality) that are the interference values of the set of nodes. In a protein network this correspond to inhibit all the selected protein at the same time in the virtual experiment.

#### 4. Click “Start” and wait for results

The computation may need a long time, depending on the size of your network. A banner and a “node worked” count appear during the computation.

## Results

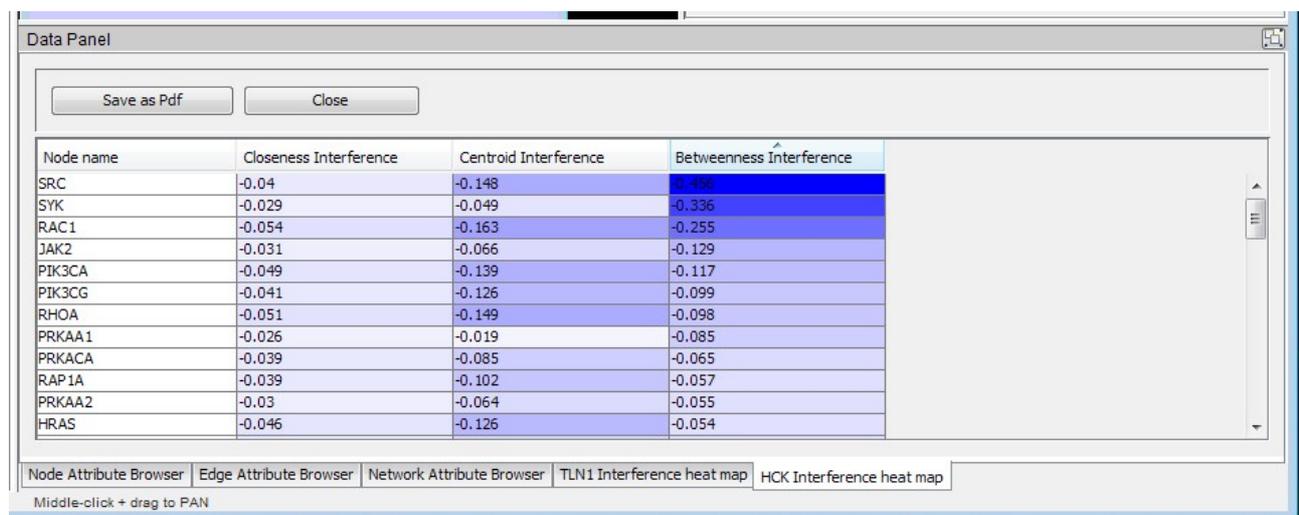
### Values as nodes attributes

Once computed, the Interference values (in percentage) are stored as node parameters and concern the single nodes. So they will appear on the Data Panel as node attributes. Using the Node attribute browser you can select one or more of them as normal attributes.

Interference also calculates the min, max and mean value for each centrality. Since they are network parameters they appear on the data panel on the Network attribute browser.

As for the other attributes you can save and load Network and Node parameters to/from a file.

### Heat maps



Node name	Closeness Interference	Centroid Interference	Betweenness Interference
SRC	-0.04	-0.148	-0.455
SYK	-0.029	-0.049	-0.336
RAC1	-0.054	-0.163	-0.255
JAK2	-0.031	-0.066	-0.129
PIK3CA	-0.049	-0.139	-0.117
PIK3CG	-0.041	-0.126	-0.099
RHOA	-0.051	-0.149	-0.098
PRKAA1	-0.026	-0.019	-0.085
PRKACA	-0.039	-0.085	-0.065
RAP1A	-0.039	-0.102	-0.057
PRKAA2	-0.03	-0.064	-0.055
HRAS	-0.046	-0.126	-0.054

Figure 2:

In the Data Panel of Cytoscape appear also a new “Heat map panel” as in figure 3 . It contains an Heat map of the computed interference value. Positive values are

highlighted in blue and negative value are highlighted in red. They can be sorted in ascending or descending order by clicking on the corresponding column header. The heat-map can be exported also in pdf format (“save as pdf” button).

## Results Panel

A detail of a CytoScaPe result panel is shown in figure 3.

The Interference result panel shows you a slider for each centrality that has been selected. The threshold is initialized to the mean value of each interference value and all the node that have a interference value less or equal to the threshold are highlighted in the network view. So if you have selected only one centrality interference all the node that have a value less or equal the threshold for that centrality are highlighted.

If you have selected more than one centralities you can decide to combine their interference values with an AND or an OR operator:

- If you select the AND operator the node for which all the value are less or equal the threshold are highlighted.
- If you select the OR operator the node for which at least one value is less or equal the threshold are highlighted

You can also deactivate one or more centralities if you do not need them, clicking on the corresponding check-box. You can also select to highlight the nodes that are more/equal than the threshold selecting the corresponding button for each centrality. Therefore you can select the more/equal option for some centralities, the less/equal option for others and can join them with the AND or the OR operator. If you need to be more precise you can modify the threshold writing the number in the corresponding text pane and then clicking the 'update' button. The 'restore' button will reset the threshold to the mean value.

## Plot by node option

When you have highlighted the nodes you are interested in, you can also select one of them and to have a graphical view of all its interference centrality values. You have to select it in the combo box and to click on the plot button. In figure 4 is shown the graphical output for the node ACTN1 in an example network. All the Centralities have been selected. The bar graph shows the mean value (blue), the min value (green), the max value (white) and the node value (red). If you select one bar of the graph the exact value will appear.

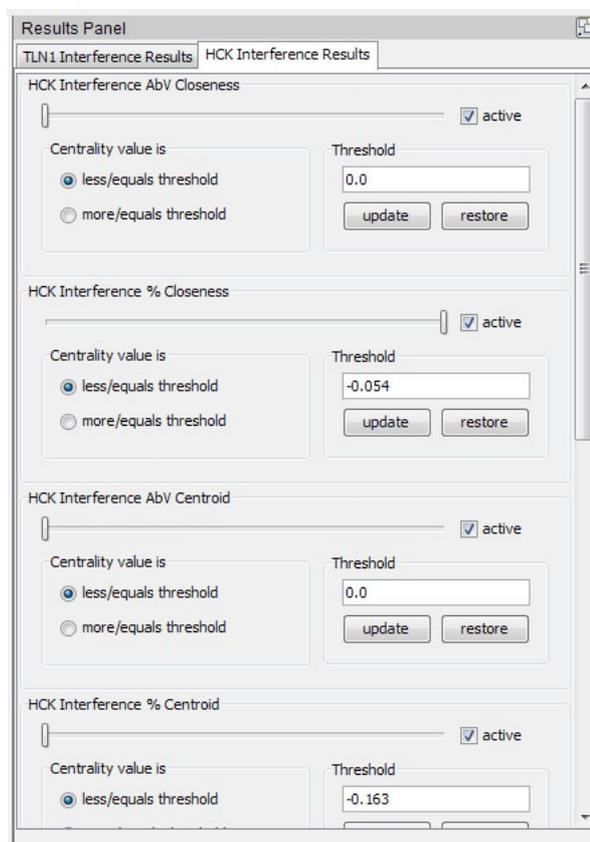


Figure 3:

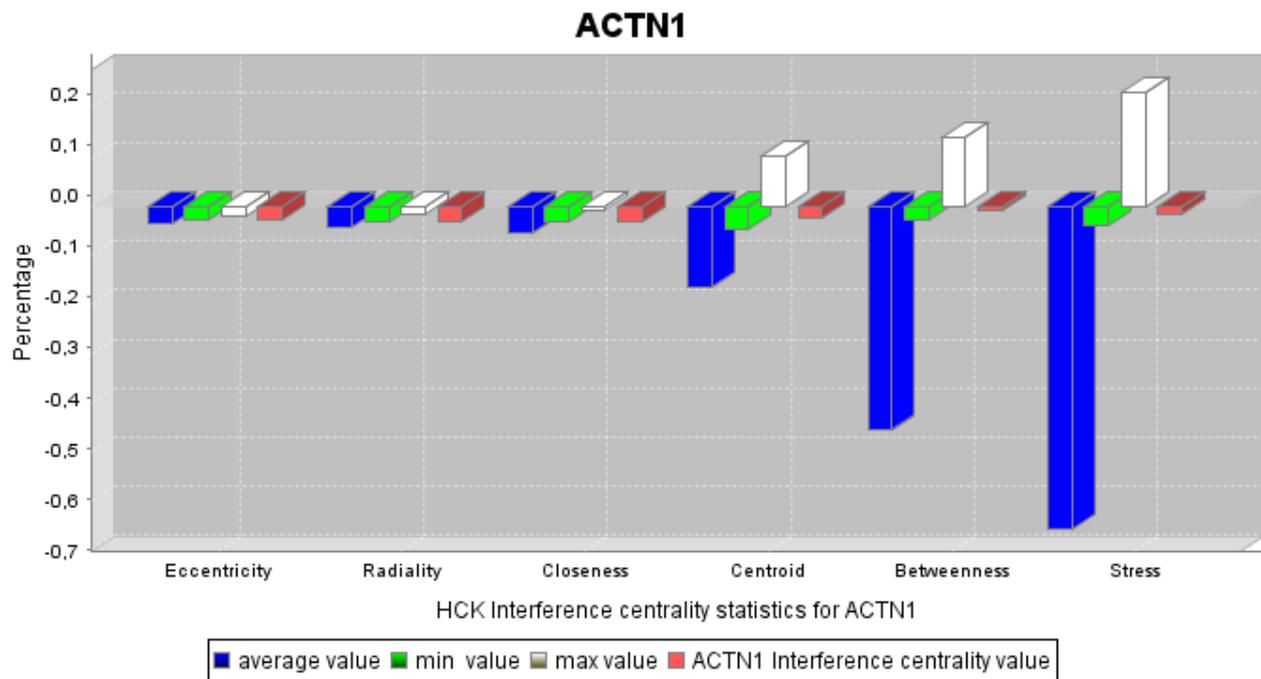


Figure 4:

## Plot by centrality option

The plot by centrality visualization is an easy way to discriminate nodes that are relevant in the network for two selected parameters. It results in a chart where there is

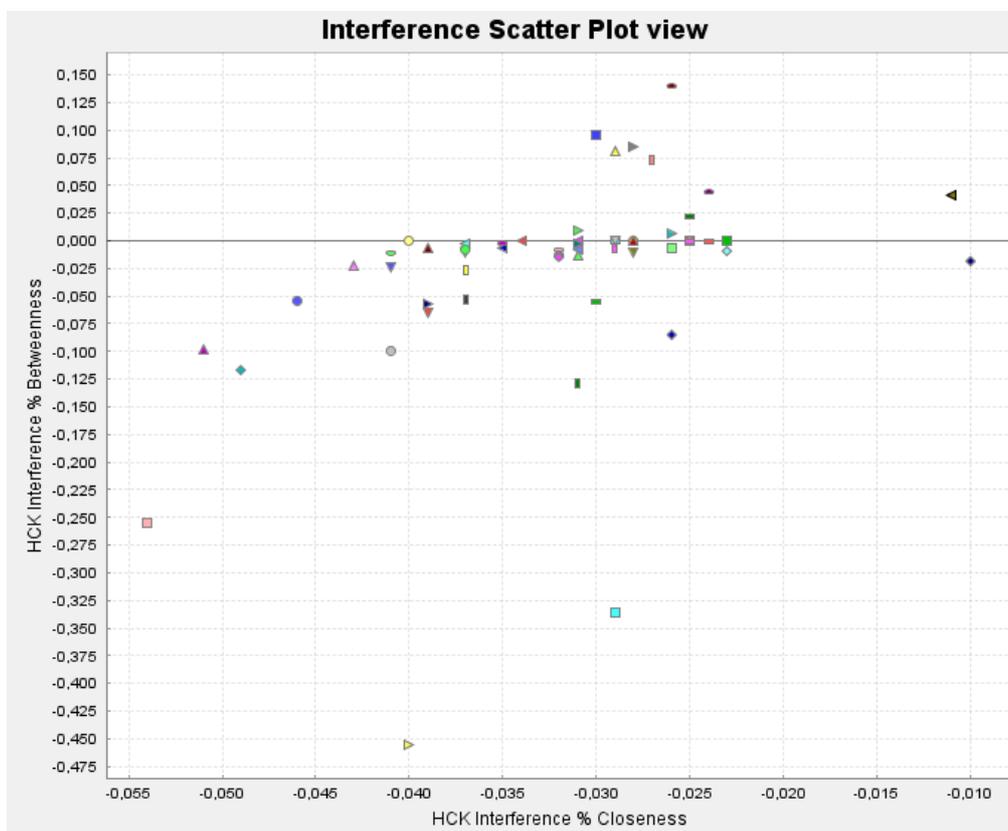


Figure 5:

an attributes on the horizontal axis and another attributes on the vertical axis. You can select one of the calculated centralities and another generic attributes or also two centralities. The plot by centrality shows clearly the distribution of the two selected attributes value in the network (see Figure 5).

- nodes having high values for both attributes are in the top right corner
- nodes having one attributes with an high value and the other with low value are in the top-left corner or in the bottom-right corner
- nodes having low values for both attributes are in the bottom left corner
- nodes with both values around the mean are in the middle of the graph

Passing with the mouse on one node in the graph its identifier appears. In the figure there is an example with Betweenness in the vertical axis and Closeness in the horizontal one. The nodes having high values for both Betweenness and Closeness Interference are easily identified in the top right corner of the chart.

## Bugs/Feature Requests

If you encounter a bug with this plugin, have a feature suggestion, or you have any question about the interference notion, we encourage you to use the Cytoscape-discuss:

<https://groups.google.com/group/cytoscape-discuss>

or the Cytoscape-helpdesk:

<https://groups.google.com/group/cytoscape-helpdesk>

mailing-list or to write an e-mail to:

[giovanni.scardoni@gmail.com](mailto:giovanni.scardoni@gmail.com)

Updates regarding this plugin will be posted to the Cytoscape-announce mailing list. You can subscribe to the mailing list or browse the archives at:

<http://groups-beta.google.com/group/cytoscape-announce>.

## Contacts

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