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Analysing Biological Networks with Cytocape

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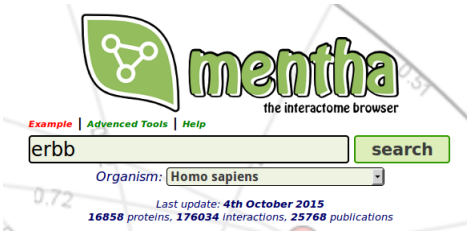
Introduction

This training session is focused on protein-protein interaction networks and on how to analyse them applying the notions given during the lecture on Graph Theory. We are going to retrieve interaction information from an online resource that integrates data from different external databases and we are going to use this data to present properties of interest, such as interaction reliability score.

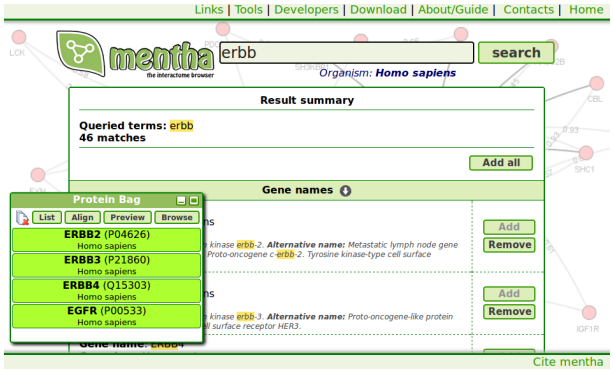
Analysing Biological Networks with Cytocape

In this training session we will use Cytoscape to analyse the ERBB protein family members and their interactors. We will use Cytoscape features to investigate and visualise information such as: Number of evidence supporting each interaction, and interaction reliability scores proportional to the experimental evidence available.

1. Go to the "mentha" database: http://mentha.uniroma2.it
2. Type "erbb" in the search field and select *Homo sapiens*, then click "Search".



3. In the "Results Page" add ERBB2, ERBB3, ERBB4 and EGFR (also known as ERBB1) to the "Protein Bag" and click "List". A list of all interactions involving one of the ERBB proteins will appear.



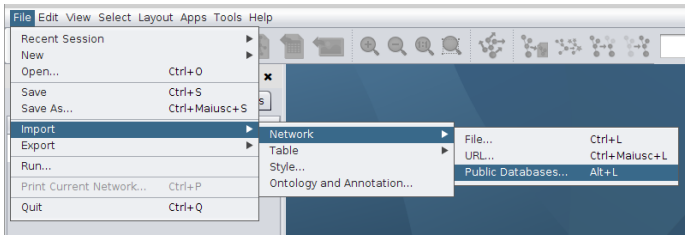
4. Export the entire list of interactions by clicking “Simple”.

Export all results: simple | with enzymatic (SLOW!)

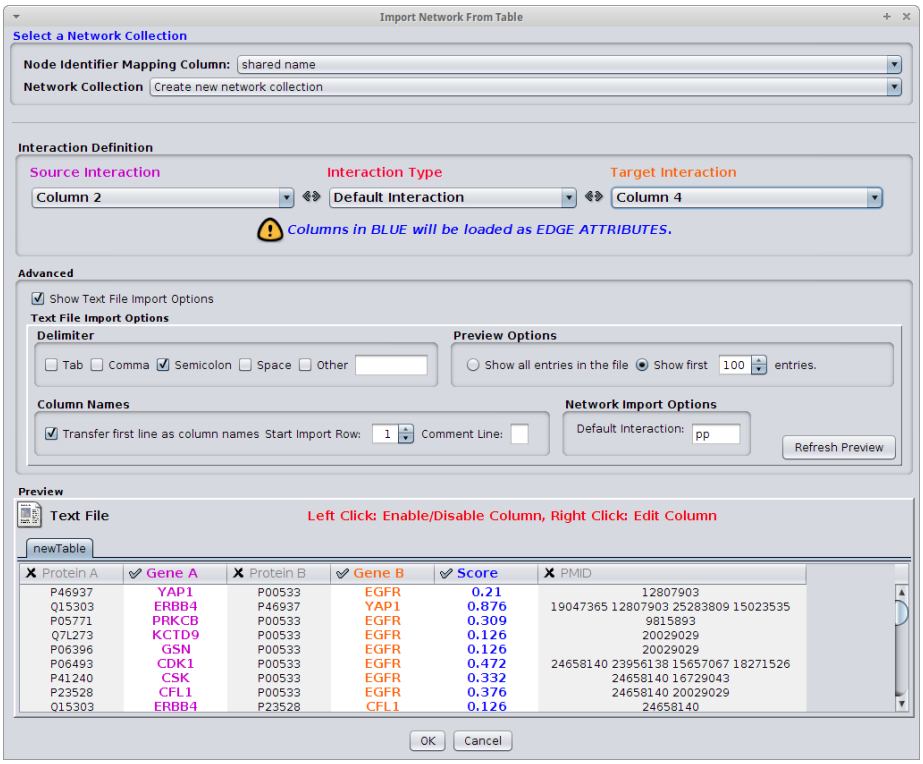
5. Now, depending on your browser save this page to a text file on your computer. For instance, in Firefox you need to click the menu icon on the right and select “Save Page”, give it a name you remember, e.g. “**erbb-interactions.csv**”.

6. Open Cytoscape.

7. We will now import interactions from the file you saved in step 5. Go to “File...” in the top menu “File” → “Import” → “Network” and select the file you save earlier.



8. To import a text file you need to tell Cytoscape how to handle your file. After you check “Show Text File Import Options”, specify as “Delimiter” semicolon. Check “Transfer first line as...” to capture column headings. Set “Source Interaction” Column 2, where gene names for A are reported. Do the same for “Target Interaction” but select Gene B. Click on the column “Score”, it will become blue and it will be loaded as interaction attribute. Finally, click “OK”.



9. Click  to layout your network in a more pleasant way.

10. Now we are going to filter only interactions with a score higher than 0.4.

11. Click on “Select” tab and add a new condition clicking the “+” sign and “Column Filter”.

12. Select “Edge: Score” and set the interval between 0.4 and 1.0 (Cytoscape may be localised in your own language, pay attention to what decimal separator you use, either full-stop or comma). The filter should be applied automatically and some edges in your network should now be coloured in red (Selected edges).

13. Create a new network using only selected nodes (File → New → Network → From selected nodes, selected edges) (If you are using a version of Cytoscape lower than 3.2, you first need to click “Select” → “Nodes” → “Nodes connected by selected edges”)

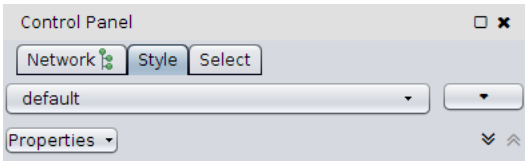
14. You can now use the “Tools” → “NetworkAnalyzer” → “Network Analysis” → “Analyze Network” to see network topological features (Your network is undirected).

Metric	Observed Value
Average Degree	
Average Path Length	
Average Transitivity (Clustering Coefficient)	

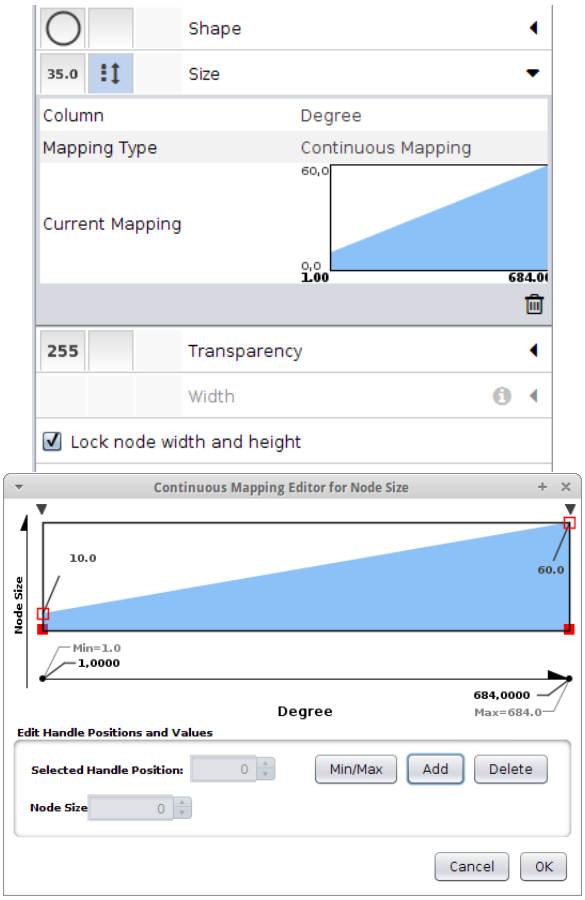
What is the clustering coefficient? The average path length? Would you say it is a "Natural Network" according to the definitions given during the "Introduction to Graph Theory" session? Observe, for instance, Degree Distributions and try "Fit Power Law" (Natural Networks are said to have an exponent between 2 and 3).

15. "Hubs" are nodes with very high degree (number of links). What nodes do you think are "hubs" in you network? Find "Hubs" in "Table Panel" sorting by degree.

16. Now we would like our visualisation to communicate some information such as "Degrees" and "Interaction Reliability Score". To this end, we are going to assign to each node a size proportional to its degree and to each link a colour proportional to its reliability score. Go to "Style" tab.



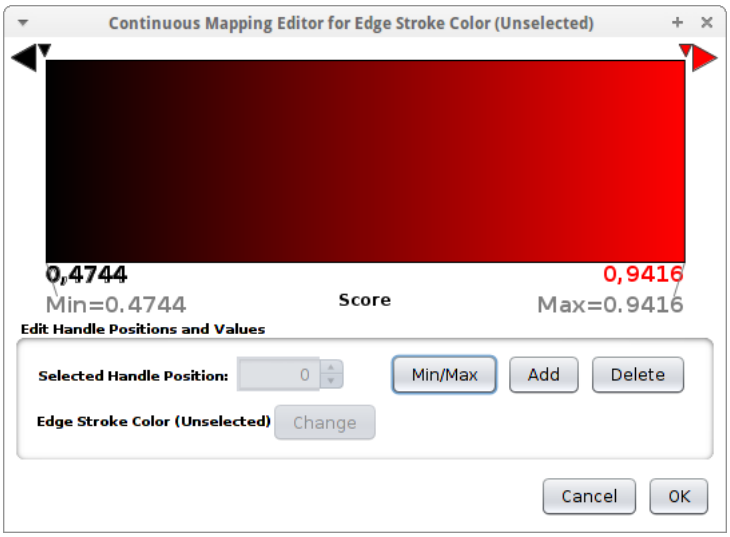
17. Check the "Lock node width and height". Double-click on the rounded rectangle beside "Shape" and select "Ellipse". Click on the little triangle beside "Size". Set "Column" to "Degree". Set "Mapping Type" to "Continuous". Double click on the blue chart and set as minimum 10 and maximum 60 by double clicking the red empty rectangles you see on the chart. Close this window.



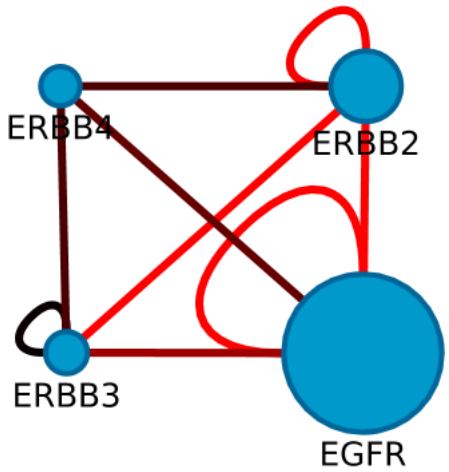
18. Now go to "Edge" tab at the bottom of the Style panel.

19. Set "Stroke Colour" on "Score" and "Continuous" mapping.

20. Double clicking "Current mapping" you can change colour gradients. Double click on the top white triangle to change its colour, do the same for the right pointing triangle and set both to red; you should obtain something similar to the following image.



21. Playing with this setting you can highlight properties without looking at the actual numeric results of "Network Analysis". For instance, you can now see that EGFR had more reported partner interactors compared to other ERBB proteins and you can also see that, despite the fact that ERBB proteins can form homo and etero dimers trimers and teramers, they actually do not have high scores for each of these combinations. You can play around with other sub setting or graphical features to highlight different aspects of this network. Try selecting only ERBB proteins and creating a new network.



22. If you finish earlier you can download other interactions and try to use filters and styles to visualise your finding.

Conclusions

Starting from a collection of proteins you now know how to collect protein interaction information and how to extract a network from them. You now know how to import such networks to Cytoscape and how to analyse their characteristics. Finally, you are able to assign to different properties different attributes, such as colours, to highlight specific characteristics, like best interaction partners.