

## Abstract

MetScape is a Cytoscape <<http://cytoscape.org>> plugin which is used to visualize and analyze metabolomic data. A number of public sources contain information about human metabolic networks consisting of compounds, chemical reactions, pathways, enzymes and genes like KEGG, and EHMN. In MetScape, we use EHMN, a high-quality human metabolic network manually reconstructed by integrating genome annotation information from different databases and metabolic reaction information from literature (Ma et al. 2007), which contains almost 3000 reactions involved in about 70 pathways.

MetScape allows users to visualize networks of compounds and display related information about reactions, enzymes, and pathways. In order to identify and quantify metabolites that are present in a cell or tissue at a given moment and under particular conditions, MetScape provides feature that users can upload their own experimental metabolomic data and visualize and explore the network over time or conditions by changing node color and/or node size using a modified DynamicXpr Cytoscape plugin. MetScape allows you to display the entire metabolic network or pathway-specific sub-networks. You can apply a pathway filter to a network and create sub-networks from resulting subsets of compounds.

In the future, we will integrate MiMI (Michigan Molecular Interactions) <<http://mimi.ncibi.org>>, a database of gene, gene product, interaction and pathways, to show gene related information developed by National Center for Integrative Biomedical Informatics.

## Visualization of Compound Networks

Figure 1 shows the whole compound network from Edinburgh Human Metabolic Network database with 2685 compounds (2621 main compounds) involved in 70 pathways. In addition, The reactions, enzymes and pathways information is shown on data panel.

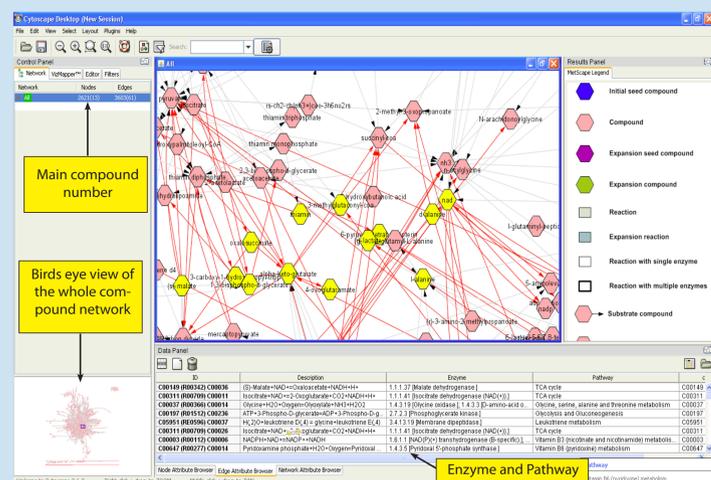
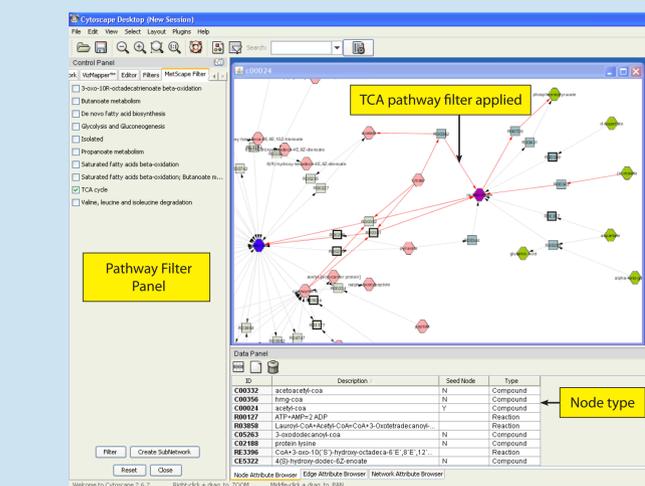


Figure 2. Network for the compound Acetyl-CoA. In this network, compound Acetyl-CoA participates in 33 reactions which involve in 10 pathways. The highlighted edges (pink lines) are the result of applying the pathway filter for the TCA-cycle.

- Blue hexagon is a seed compound, pink hexagons are compounds that participate in the same reactions as seed compound does.
- Clicking on a non-seed compound will expand network with other reactions that the compound may involve in.
- Reaction node with bold border means multiple enzymes involve in the reaction. Reactions with regular border means single or no enzymes involve in.



## Experimental Data

MetScape allows users to upload their own metabolomic experiment data.

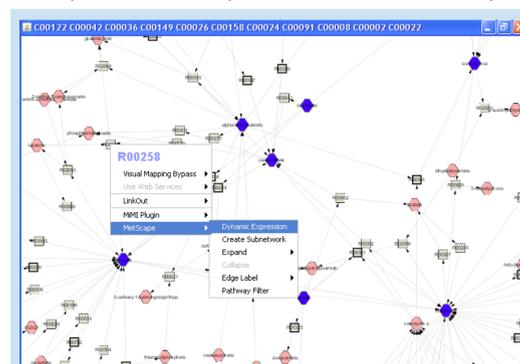


Figure 3. shows network with compounds from Dr. Charles Burant's metabolic experiment file as seed compounds. The file contains 11 compounds (blue hexagon) and corresponding values at 5 different moments and conditions.

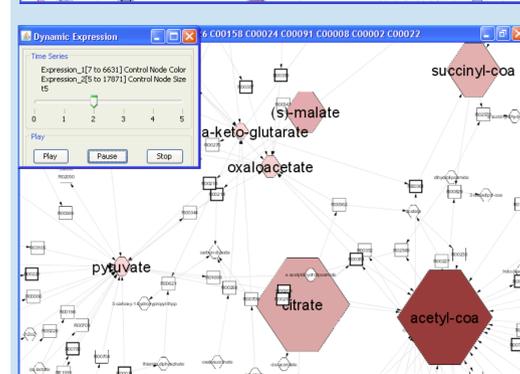


Figure 4. Shows the compounds values by changing the node color and node size at specific time and condition in the network on Figure 3. Users can play a movie (modified dynamicXpr plugin) to see the node color and size changes at different times and conditions.

## Recent Feedback

Here are how scientists using MetScape in their research:

- Carlo Laudanna**, Professor, Department of Pathology, Division of General Pathology, University of Verona, Italy  
"We are using Cytoscape with MetScape to analyze metabolomic data derived from NMR studies. Basically, we are studying the metabolomic signature of human primary T-lymphocytes stimulated with chemokines in presence of different specific signaling inhibitors. Then, we wish to reconstruct metabolic networks by using MetScape and infer context-specific metabolic regulation".
- Christopher Beecher**, Research Professor, Michigan Center for Translational Pathology  
"I plan on using it to find patterns that are hidden in the fairly compact but complex metabolomic dataset. Another way to say it is MetScape allows me to cast metabolomic data into biochemical context".
- Charles Burant**, Professor, Departments of Internal Medicine and Human Genetics, University of Michigan  
"...The web interface is linked to Cytoscape to build and display the network, using several customized layouts. Once the network has been displayed in Cytoscape, the user can import the normalized experimental metabolite data. Several data points can be loaded; the color and shape of the nodes are used to represent different parameters. The plug-in allows users to cycle through the data points sequentially, while the underlying network remains unchanged".

## MetScape Availability

MetScape v0.8 (Beta) was released to Cytoscape on March 13, 2009. There are three ways to launch MetScape:

- Install MetScape from within Cytoscape.
  - Plugins → Manage Plugin → "Network and Attribute I/O" category.
  - \*\* Easy to update
- Launch MetScape using Java Web Start (Cytoscape not required to be installed)
  - <http://mimi.ncibi.org> → MetScape Link
- Download MetScape jar
  - from Cytoscape plugin website ([http://chianti.ucsd.edu/cyto\\_web/plugins/index.php](http://chianti.ucsd.edu/cyto_web/plugins/index.php)) under "Network and Attributes I/O" category and store it in your cytoscape plugins directory.

Get Cytoscape at: [www.cytoscape.org](http://www.cytoscape.org)

**There are more than 150 downloads and is growing.**

## Database Structure

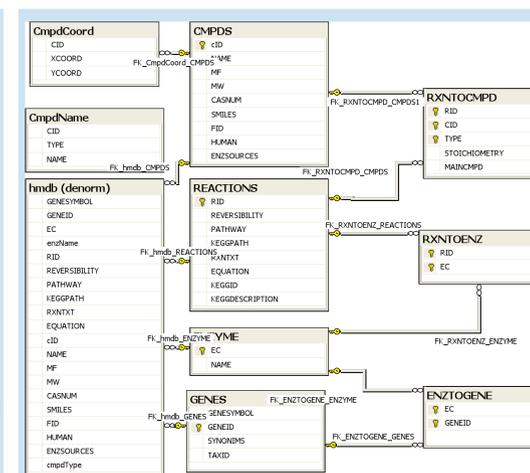


Figure 5. shows the HUMDB database structure on our sql server database server. The database contains compound, reaction, enzyme and gene tables, and mapping tables of compound to reaction, reaction to enzyme, and enzyme to gene. There are total 2844 reactions, 16440 compounds (2686 compounds participate in reactions), 5138 enzymes (869 enzymes involve in reactions), 2231 genes (corresponding to enzymes).

## MetScape Features

- Retrieve compound networks from EHMN metabolic database
- Provide two styles of networks
  - Compound and reaction are shown as nodes which is good at displaying compound network
  - Compound is shown as node and reaction is shown as edge which is good at displaying pathway
- Show networks with only main compounds or all compounds
- Display compound network and related reaction, enzyme and pathway information
- Expand and collapse compound network
- High light all compounds that involve in a reaction when put mouse over the reaction
- Create sub-network for highlighted nodes/edges
- Upload users own metabolomic experiment data and show compound network over time or condition by changing node color and/or node size (using modified dynamicXpr Cytoscape plugin)
- Display entire metabolomic network or pathway-specific sub-network
- List all pathways related to certain compound network and allow users to do pathway filter and generate pathway-specific sub-networks
- Show compound and reaction detail pages by linking out to MiMI WEB
- Show or hide edge labels
- Create compound lookup table for users to explore all compounds from EHMN local database. Users are able to copy and paste compounds from lookup table to search box and retrieve network.

## Future Plans

- Allow Compound Name Search
  - Only primary name or primary name and synonym
  - Auto complete name input
- Provide Compound Structure
  - When user click a compound, show the compound structure on result window of Cytoscape
- Integrate with MiMI Database and other NCIBI tools
  - Show gene information associated with compound
  - Create bipartite network of compound reaction and protein interaction
  - Use directional edge to represent the information flow of network
  - Integrate MetScape with Metab2Mesh and other related tools
- Integrate subcellular localization with HUMDB

## References

- Ma H, Sorokin A, Mazein A, Selkov A, Selkov E, Demin O, Goryanin I. The Edinburgh human metabolic network reconstruction and its functional analysis. *Mol Syst Biol.* 2007;3:135.
- Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B, Ideker T. Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Research* 2003 Nov; 13(11):2498-504
- Gao J, Ade AS, Tarcea VG, Weymouth TE, Mirel BR, Jagadish HV, States DJ. Integrating and annotating the interactome using the MiMI plugin for cytoscape. *Bioinformatics.* 2009 Jan 1;25(1):137-8.
- Tarcea VG, Weymouth T, Ade A, Bookvich A, Gao J, Mahavisno V, Wright Z, Chapman A, Jayapandian M, Ozgur A, Tian Y, Cavalcoti J, Mirel B, Patel J, Radev D, Athey B, States D, Jagadish HV. Michigan molecular interactions r2: from interacting proteins to pathways. *Nucleic Acids Res.* 2009 Jan;37 (Database issue): D642-6.
- DynamicXpr plugin for Cytoscape <http://www.rbvi.ucsf.edu/Research/cytoscape/>

## Funding Acknowledgements

This work was supported by grant U54 DA021519 from NIDA, National Institutes of Health.