

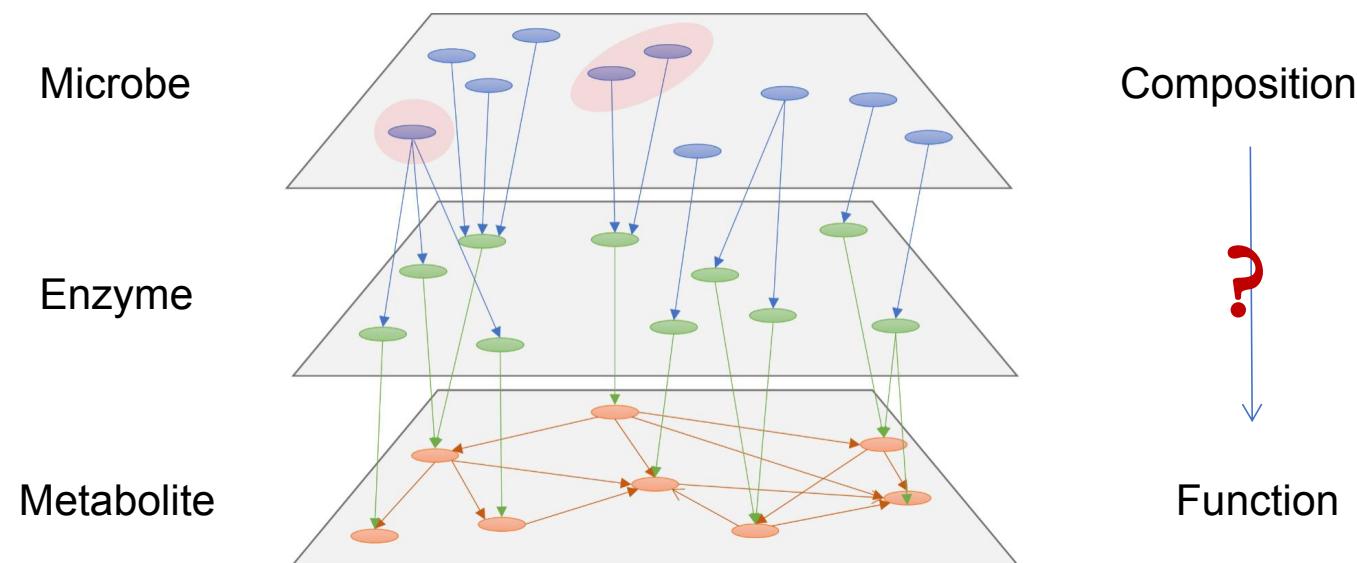
OmicsNet Tutorial: Build network from a taxon list

Computer Requirement

- Modern browser supporting WebGL
- Chrome 50+, Firefox 47+, Safari 10.1+ and Edge 12+
- Please make sure WebGL is enabled in your browser
 - Please consult this web page to verify: <https://get.webgl.org/>
- If not enabled, please consult our FAQ page for instructions
- For best performance and visualization, use:
 - Latest version of Google Chrome
 - A modern computer with at least 4GB of physical RAM
 - A 15-inch screen or bigger (larger is better)
 - Retina Display is supported

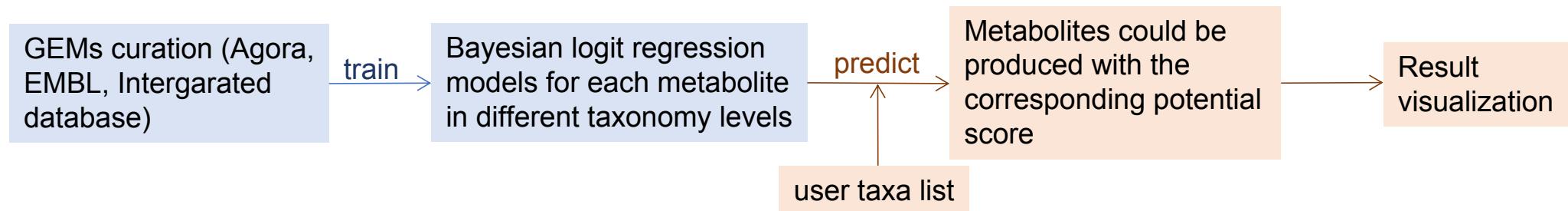
Motivation

Microbiome is known to be involved in numerous host health effects ranging from host responses to cancer immunotherapy to metabolic disease and obesity. Metabolites produced by microbes are direct players in host-microbe interaction triggering downstream signals. Inferring the microbial metabolite features can facilitate the discovery of novel taxon-metabolite associations or serve as testable hypotheses for microbiome-metabolomics integration thus help to understand the underlying mechanism between host-microbiome crosstalk. However, tools that can predict microbial metabolites from a given microbiome are still lacking.



Overview

- **Goal:** This module is designed to decipher the metabolite production potential of the user interested taxa list to help understand the role of microbiome (currently focusing on human gut microbiome) in specific biological conditions.
- **Method and Procedure:**



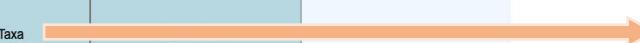
- GEMs: Genome-scale metabolic models, describe the detailed microbial metabolism at strain level that can serve as knowledge background for model training.
 - Bayesian logit regression model: provide the probabilities for classification of certain taxon as a producer of given metabolite
 - Potential score: a prediction value based on Bayesian logit regression models indicating the possibility of a specific taxon to produce a given metabolite.
-
- **Result:** The prediction result will be present by either a composite network or an interaction heatmap for visualization and analysis

Data Upload

Multi-omics Integration via Biological Networks

Objective	Click on a panel below to start					
Explore networks in 2D or 3D space			A Graph File			
Annotate SNPs, taxa, or LC-MS peaks for network analysis		SNPs	Microbial Taxa			
Network analysis of one or more list(s) of molecules	Genes	Proteins	Transcription Factors	miRNAs	Metabolites	

Proceed **Reset**



Users can upload a **taxa list** from a specific taxonomy, e.g. a list of dysregulated taxa or the taxonomy annotation of the sequencing samples.

By selecting from the drop-down menu, users need to specify the **taxonomy level** which is necessary for the function prediction. 7 different levels are provided ranging from phylum to strain.

The **abundance** is optional. If it is not provided, 1 will be used as default value.

Upload a list of taxon names

Enter your data below: ?

Taxon Name Level: **Species Name** ▾

```
Faecalibacterium_prausnitzii
Bacteroides_uniformis
Eubacterium_rectale
Alistipes_putredinis
Subdoligranulum_unclassified
Escherichia_coli
Bacteroides_vulgatus
Clostridium_clostridioforme
Klebsiella_pneumoniae
Clostridium_hathewayi
Alistipes_shahii
Ruminococcus_obeum
Roseburia_inulinivorans
Bacteroides_thetaiotaomicron
```

Use our example data

Upload **Cancel**

Database Selection

To construct the metabolic functional network from the input taxa list, user need to specify parameters to decide the metabolites involved including:

- **GEMs database:** used to predict the metabolite produced and their corresponding potential scores
- **Threshold for potential score:** score over 0.5 indicates the taxon is more likely to produce the given metabolite and the increasing score value means the greater production possibility.
- **Exclude metabolites:** users can choose to exclude currency metabolites, universal metabolites or the metabolites without pathway annotation

Database Selection

Databases are organized under different tabs. Please choose proper database(s) for network creation based on your analysis objectives. Multiple types of networks will be merged (based on shared nodes) and customized in the next page

Taxon-metabolite

Predicting Metabolic Potential of Microbial Taxa

The prediction is obtained based on logistic regression models trained based on high-quality genome-scale metabolic models (GEMS). The taxon-metabolite network could be further enriched by introducing protein-metabolite to find out potential enzymes. In the network viewer, you can click on icon located in the vertical toolbar for overview of the potential scores across all metabolites for your input taxa.

AGORA AGORA GEMS (potential scores for 1110 metabolites)
EMBL EMBL GEMS (potential scores for 930 metabolites)

Potential score: 0.9

Excluding:
 Currency metabolites
 Universal metabolites
 Metabolites without pathway annotation

Currency metabolites: abundant substances such as water and carbon dioxide known to occur in normal functioning cells.
Universal metabolites: include currency metabolites and other metabolites shared across all taxa based on the GEMS databases.

Microbial taxa	Taxon-metabolite	55 - 379 - 28	Browse	Download	Delete
Metabolite	Metabolite-protein	124 - 109 - 0			

<< Previous 1 >> Proceed

Records of the individually generated network that users can trace, browse download or deleted accordingly

Network expansion

In the **database selection page**, users can also expand the taxon-metabolite network:

The taxon-metabolite network can be extended to include Metabolite-protein interactions by querying the related microbial databases.

Database Selection

Databases are organized under different tabs. Please choose proper database(s) for network creation based on your analysis objectives. Multiple types of networks will be merged (based on shared nodes) and customized in the next page

Metabolite-protein Taxon-metabolite

KEGG (Organism-specific)
 Recon3
 AGORA
 EMBL
 KEGG Generic

Metabolite-protein interaction data based on all KEGG reactions (updated on 01/04/2022)
High-quality genome-scale metabolic reconstruction (human) (updated on 01/04/2022)
Agora based microbial metabolic reactions (updated on 01/12/2022)
EMBL GEMS based microbial metabolic reactions (updated on 01/12/2022)
Non-organism specific metabolic reactions from KEGG metabolic network (updated on 01/04/2022)

Submit

Individual Omics Networks

Each network is created independently by searching input list against a selected database. The network usually contains several disconnected subnetworks.

Input Type	Network Type	Sizes (node# - edge# - seed#)	Browse	Download	Delete
Microbial taxa	Taxon-metabolite	55 - 379 - 28			
Metabolite	Metabolite-protein	124 - 109 - 0			

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Users can trace the networks built in different types individually.

Network interaction table

For each individual network, an interaction table is provided for users to dig into the details of their query results in :

Individual Omics Networks

Each network is created independently by searching input list against a selected database. The network usually contains several disconnected subnetworks.

Input Type	Network Type	Sizes (node# - edge# - seed#)	Browse	Download	Delete
Microbial taxa	Taxon-metabolite	55 - 379 - 28			
Metabolite	Metabolite-protein	124 - 109 - 0			

Note: Query ID list is the input taxon for the first network and result metabolites can be used as queries in the following networks, and so forth.

Individual Network Interaction Table

You can browse, search or manual delete an interaction (edge), or use the Advanced Filter to exclude a node (and its all associated edges).

Advanced Filter

Id1 ↑	Query ID	Id2 ↑	Result ID	Name1 ↑	Query Name	Name2 ↑	Result Name	Action
Roseburia hominis	C04691	Roseburia hominis		2-Dehydro-3-deoxy-D-arabino-heptonate 7-phosphate				Delete
Roseburia hominis	C02637	Roseburia hominis		3-Dehydroshikimate				Delete
Roseburia hominis	C03232	Roseburia hominis		Phosphohydroxypyruvic acid				Delete
Roseburia hominis	C01269	Roseburia hominis		5-O-(1-Carboxyvinyl)-3-phosphoshikimate				Delete
Roseburia hominis	C06056	Roseburia hominis		4-Hydroxy-L-threonine				Delete
Roseburia hominis	C00979	Roseburia hominis		O-Acetyl-L-serine				Delete
Roseburia hominis	C05774	Roseburia hominis		Cobinamide				Delete
Roseburia hominis	C00522	Roseburia hominis		(R)-Pantoate				Delete
Roseburia hominis	ppg161	Roseburia hominis		Phosphatidylglycerophosphate (dihexadec-9-enoyl, n-C16:1)				Delete
Roseburia hominis	C01102	Roseburia hominis		O-Phosphohomoserine				Delete
Roseburia hominis	C02876	Roseburia hominis		Propanoyl phosphate				Delete
Roseburia hominis	C00493	Roseburia hominis		Shikimate				Delete
Roseburia hominis	C09332	Roseburia hominis		Tetrahydrofolyl-[Glu](2)				Delete
Bacteroides uniformis	C04691	Bacteroides uniformis		2-Dehydro-3-deoxy-D-arabino-heptonate 7-phosphate				Delete
Bacteroides uniformis	C02637	Bacteroides uniformis		3-Dehydroshikimate				Delete

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Users can tailor their network by deleting the results they are not interested in

Network Building

After generating the network individually, users will be lead to the summary of the integrated network:

Methods for pruning and tailoring the network for better visualization and enhanced functional interpretation

Detail topology information of the final integrated network.

Proceed for visualization

Proceed >

Network Tools ?

Degree Filter

Betweenness Filter

Minimum Network

Steiner Forest (PCSF)

Tissue Filter

P-value Filter

Zero-order Network

Reset to First-order

Multi-omics Network Building

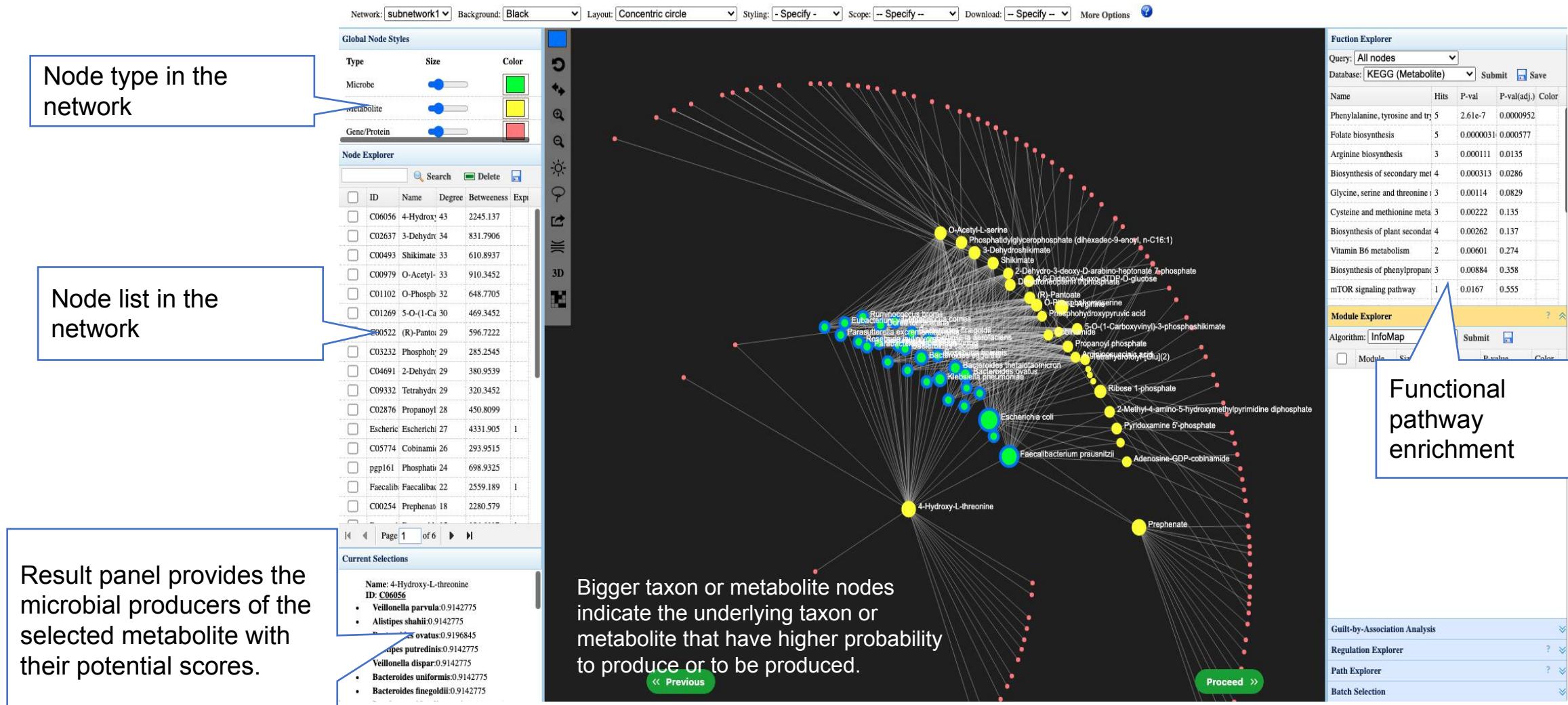
If more than one network was generated in the previous page, they are merged together to form multi-omics network through shared nodes. In some cases, the result will contain a larger subnetwork containing most of queries, and several smaller subnetworks containing one or a few queries. These subnetworks will be available for visual analysis in the next page.

If the network is too large, it is recommended to trim the network to a smaller size that is suitable for visual analytics (less than 2000 nodes), you can use network tools located on the left hand side for trimming and filtering.

Networks	Sizes (node# - edge# - seed#)	Topology	Download (edge list)
subnetwork1	420 - 966 - 28	Details	Download

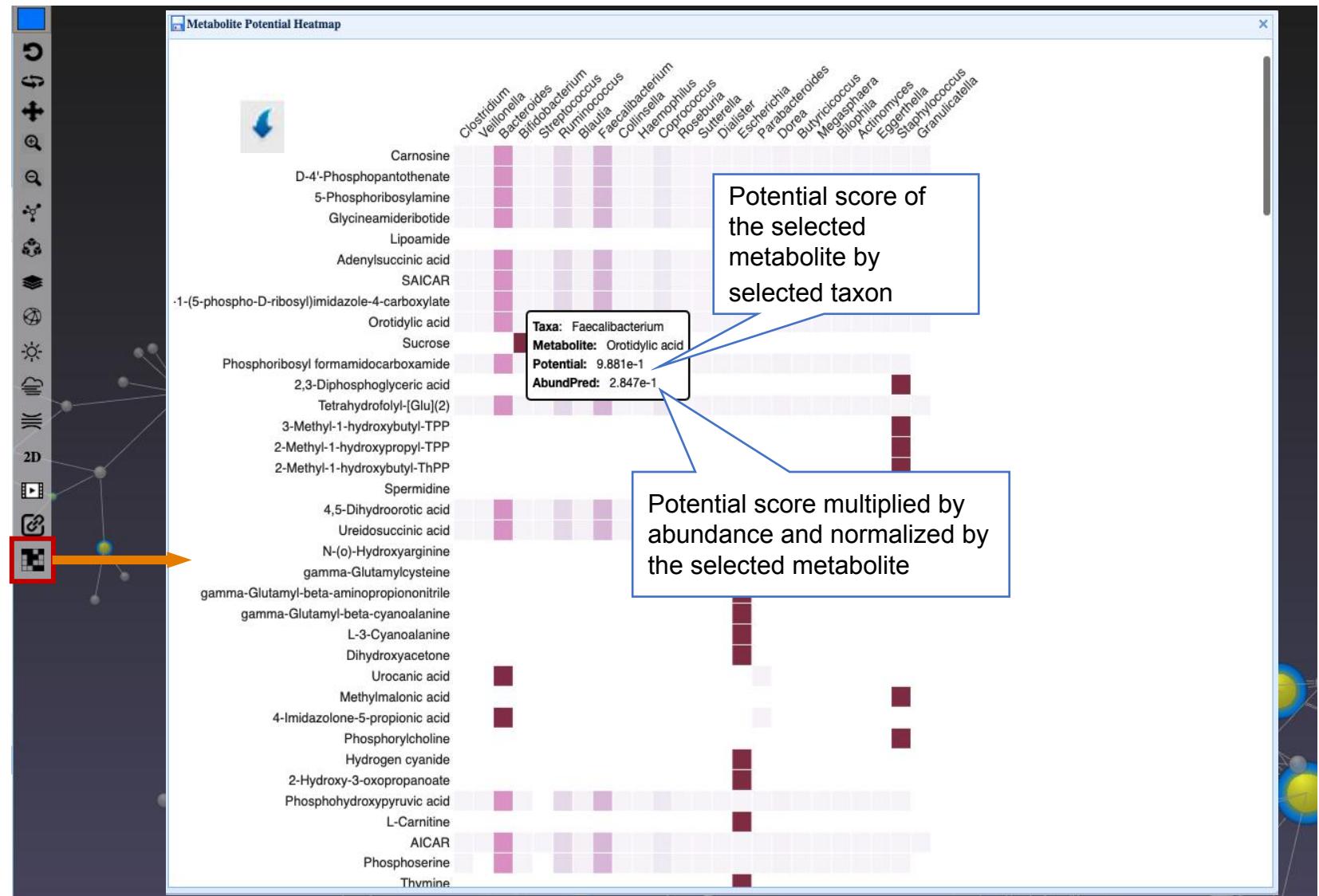
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Network Visualization



Heatmap Visualization

- Interactive heatmap is also provided for users to compare the microbial metabolic potential across taxa.
- The columns represent the interested taxa and rows are their potential output metabolites.
- The color gradient from white to dark red indicate the normalized metabolic production potential of each taxon from 0 to 1.



The End
