

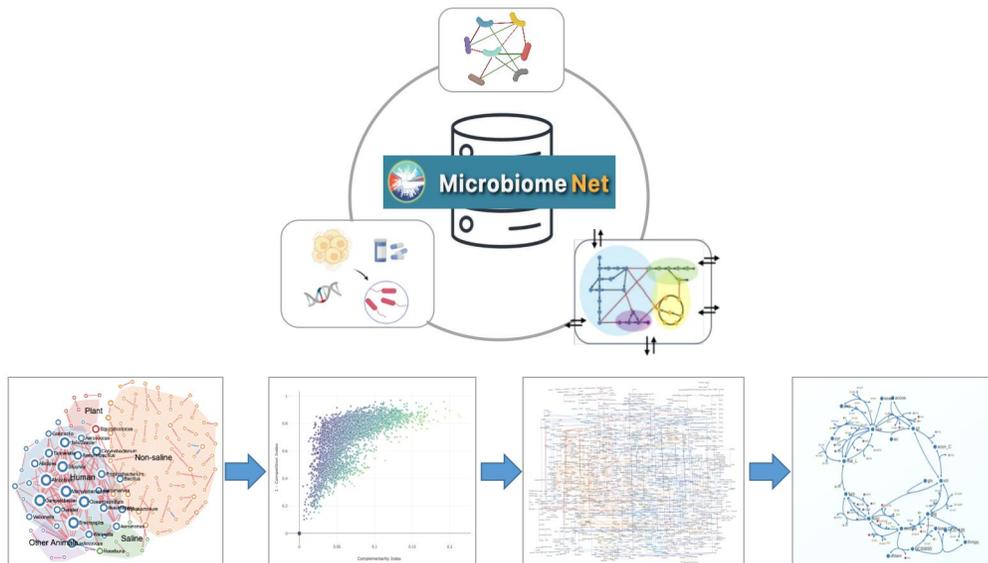
# MicrobiomeNet Tutorial

Explore microbial statistical associations and  
metabolic profiles for functional insights

2024-AUG-18

# Overview

MicrobiomeNet is a comprehensive database and visualization platform aiming to integrate microbial associations with their metabolic profiles for mechanistic insights.



## ❑ Database:

- >12,000 GEMs ( ->[Slide 23](#) )
- ~5.8M microbial interactions
- ~30K phenotype associations

## ❑ Visualization:

- metabolic network at both pathway and global metabolism levels
- microbial interaction network

## ❑ Statistics:

- Neighborhood Map ( ->[Slide 24](#) )
- Metabolism Compatibility Map ( ->[Slide 25](#) )

Refer to the corresponding slides for more details on GEMs, the Neighborhood Map, and the Metabolism Compatibility Map.

# Design

MicrobiomeNet allows intuitively mining of known microbial associations (i.e. co-occurrences patterns) within the context of their metabolite profiles (i.e. GEMs) for mechanistic insights. The underlying assumption is that the direct metabolic interactions are rare among their known statistical associations. Focusing on a query microbe, MicrobiomeNet provide the [a three-step sequential strategy](#) to identify the potential metabolic interaction among the reported statistical associations :

1. Search and identify its known co-occurrence patterns through established microbial association network based on literature .
2. Investigate metabolic patterns and paired indexes for the associated microbes through Neighbourhood Map & Metabolism Compatibility Map.
3. Visually compare the metabolic processing at global metabolism and pathway levels.

# Usage

Built around the above mentioned strategies, MicrobiomeNet supports six query categories as input, including:

- microbe: -> [Slide 5](#)
- metabolite: -> [Slide 13](#)
- enzyme: -> [Slide 13](#)
- phenotype: -> [Slide 18](#)
- gene/snp: -> [Slide 18](#)
- drug: -> [Slide 18](#)

Note:

Based on the similarity of the result page, the use case of metabolite and enzyme input are grouped together, while phenotype, gene, and drug input are grouped together.



Start from a  
microbe

# Microbe Input

Welcome to MicrobiomeNet

-- Explore microbial statistical associations and metabolic profiles for functional insights

Type your query microbe here. Select from the autocomplete list for faster and more accurate searching.

Select the type of input

Please enter an item:

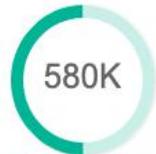
Escherichia coli

Search

Examples: #1 #2

Click to get the result summary

Use our example data for testing



Microbial Interactions

Study	Scenario	EMP Ontology
76	133	19 (emp_3)



GEMs

Genus	Species	Strain
1951	5898	12088



Pathways

Metabolite	Reaction	Enzyme
4362	7861	1800

# Result Summary

## Search Result

**Query microbe: Faecalibacterium prausnitzii**

A total of **237** microbial interaction are found for Faecalibacterium prausnitzii, including **219** positive ones and **18** negative ones. 10 GEMs at strain level were found. You can visualize and find more details by clicking icons in the summary table below.

The GEM view and pathway view for higher-level taxonomy are displayed as a combination of all GEMs within the specific taxon, as the GEMs are constructed at the strain level.

Text summary of the microbial interactions and GEMs found for the query microbe

Statistics Summary							
Microbe	Microbial interactions	GEM View	Pathway	Reaction	Metabolite	Neighbourhood Map	Metabolism Compatibility Map
Faecalibacterium prausnitzii	237  			3710 	1804 		

View statistics and hyperlinks for detailed information. Click the icons to access the results table or navigate to the corresponding visualization page.

# Microbial associations

Specify habitat and context (disease/lifestyle, only applicable for human) here

Specify method, direction and threshold to filter the network

Select and highlight an interaction on the network

Update the layout of the network here.

Metabolic interactions obtained for the query microbe. Click a node or an edge to highlight it and display detailed information.

Filter Network

Habitat: Select habitats, e.g Human, Saline

Healthy, Colon adenoma, Colon carcinoma, Prehypertension, Hypertension

Computation: All selected (8)

Direction: Both

Threshold: 0.3

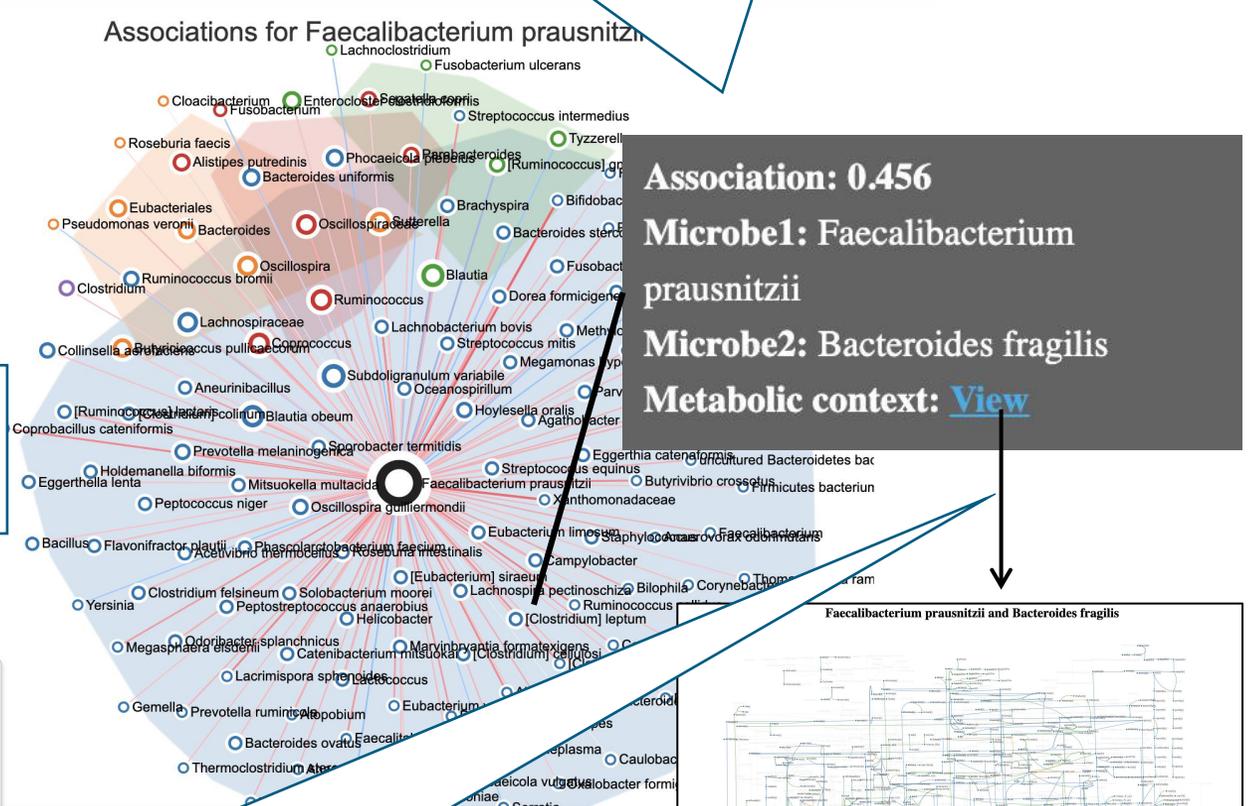
Taxonomy: All selected (6)

Update

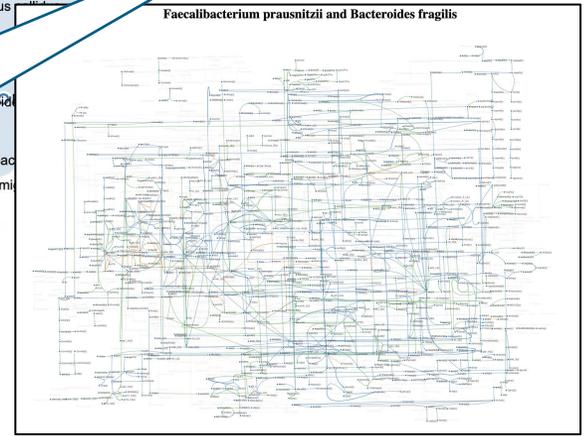
Specify taxonomy level here

Source	Target	Weight	Context	Method	
<input type="checkbox"/>	Faecalibacteriu	Subdoligranulu	0.9991	Human;Distal Gu	Pearson correla
<input type="checkbox"/>	Faecalibacteriu	Oscillospira gu	0.9967	Human;Distal Gu	Pearson correla
<input type="checkbox"/>	Prevotella mela	Faecalibacteriu	0.9959	Human;Distal Gu	Pearson correla
<input type="checkbox"/>	Hoyleseella oral	Faecalibacteriu	0.9958	Human;Distal Gu	Pearson correla
<input type="checkbox"/>	Faecalibacteriu	Sporobacter ter	0.9953	Human;Distal Gu	Pearson correla
<input type="checkbox"/>	Bifidobacteriu	Faecalibacteriu	0.9879	Human;Distal Gu	Pearson correla
<input type="checkbox"/>	Faecalibacteriu	Xanthomonada	0.9699	Human;Distal Gu	Pearson correla
<input type="checkbox"/>	Faecalibacteriu	Subdoligranulu	0.8998	Human;Distal Gu	Pearson correla

Healthy, Colon adenoma, Hypertension, Colon carcinoma, Prehypertension



Navigate to the GEM view to visually compare the metabolic capacity of the selected microbes.



# GEM view

Select at least two microbes for competition and complementarity indexes calculation ([Slide 25](#)). Use the "Filter" icon to specific the taxa.

Select to color the network by different microbes or by different pathways

Network Comparison Node Edge

Faecalibacterium prausnitzii is selected! Please use **↑** on the right to select another microbe before the index calculation.

Metabolism: Primary metabolism

Index: Competition

isGiant:

Submit

Show the seed metabolite ([Slide 25](#)) on the network

Network Comparison Node Edge

Mode: Pan

Color by: Pathway

Seed: Show

Reaction node: Hide

Background: Blue-gradient

Search pathway

Search  Clear

<input type="checkbox"/>	Pathway	Metabolism	Link	Color
<input type="checkbox"/>	Alanine and aspartate m	Amino acid	<input type="checkbox"/>	<input type="text"/>
<input type="checkbox"/>	Arginine and proline me	Amino acid	<input type="checkbox"/>	<input type="text"/>
<input type="checkbox"/>	Glutamate metabolism	Amino acid	<input type="checkbox"/>	<input type="text"/>
<input type="checkbox"/>	Glycine, serine, alanine,	Amino acid	<input type="checkbox"/>	<input type="text"/>
<input type="checkbox"/>	Histidine metabolism	Amino acid	<input type="checkbox"/>	<input type="text"/>
<input type="checkbox"/>	Lysine metabolism	Amino acid	<input type="checkbox"/>	<input type="text"/>
<input type="checkbox"/>	Methionine and cyste	Amino acid	<input type="checkbox"/>	<input type="text"/>
<input type="checkbox"/>	Phenylalanine metabolis	Amino acid	<input type="checkbox"/>	<input type="text"/>
<input type="checkbox"/>	Tryptophan metabolism	Amino acid	<input type="checkbox"/>	<input type="text"/>
<input type="checkbox"/>	Tyrosine metabolism	Amino acid	<input type="checkbox"/>	<input type="text"/>

Current selection

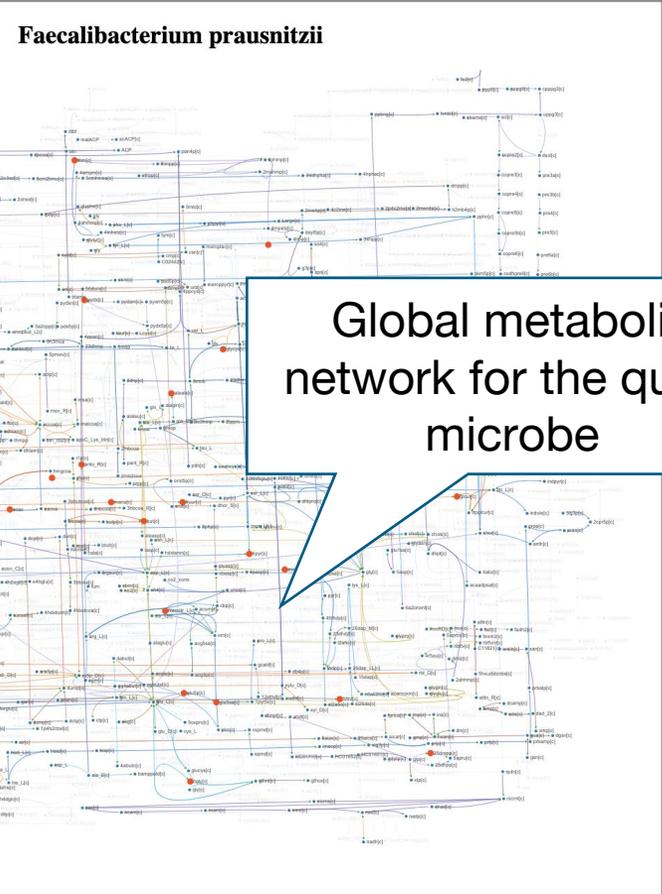
Faecalibacterium prausnitzii

Filter the metabolic network by selected taxa

Highlight the interested pathways

Click to access the pathway view

Click to change the color for each pathway



Global metabolic network for the query microbe

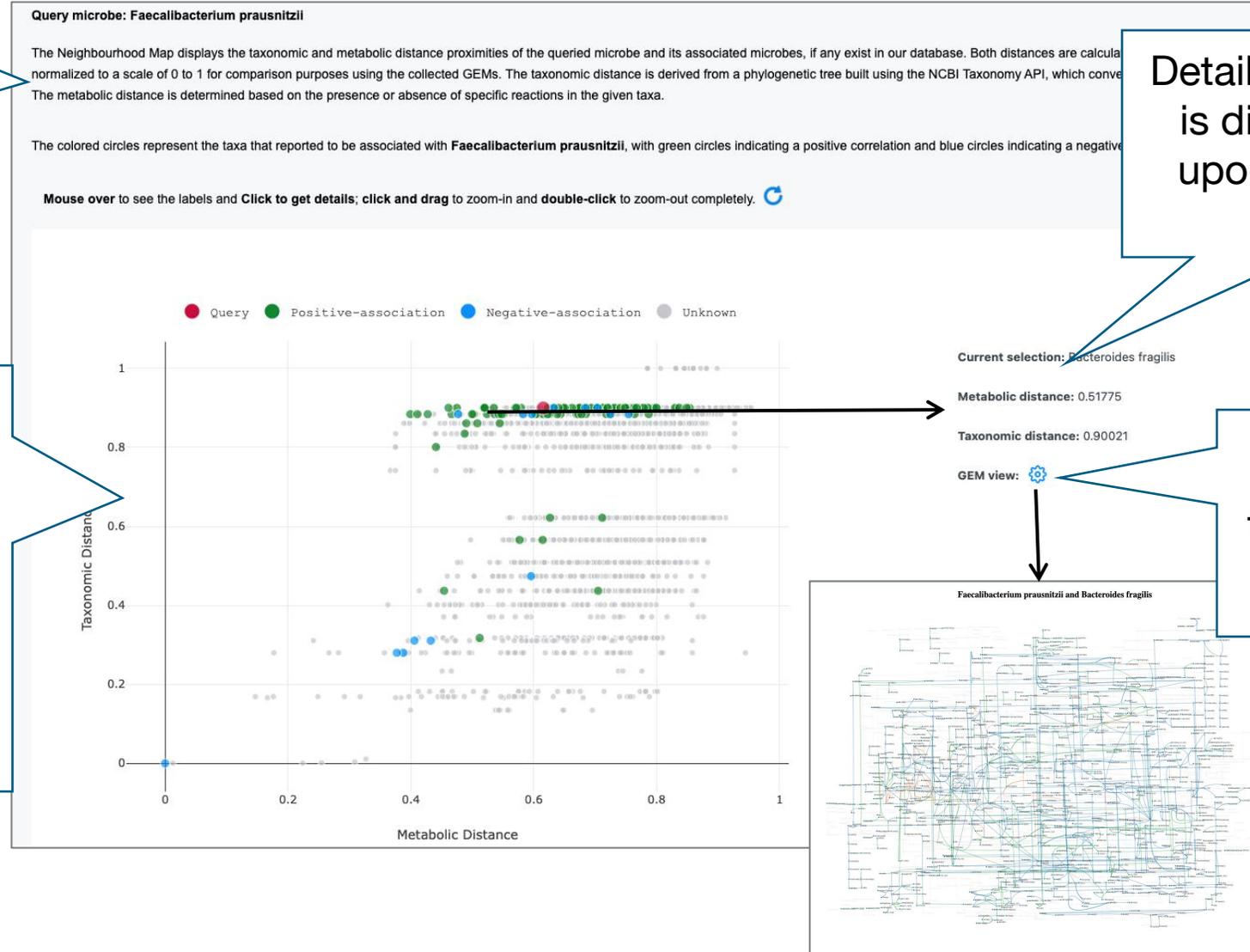
Note: The GEM view can also be accessed directly from the microbial association network, Neighborhood Map, and Metabolism Compatibility Map for comparing paired microbes.



# Neighborhood Map

Introduction to the Neighborhood Map. More explanation refer to Slide

The colored dots show the associated taxa obtained for the query microbe, with green indicating a positive correlation and blue indicating a negative correlation.



Detailed information is displayed here upon clicking the dots.

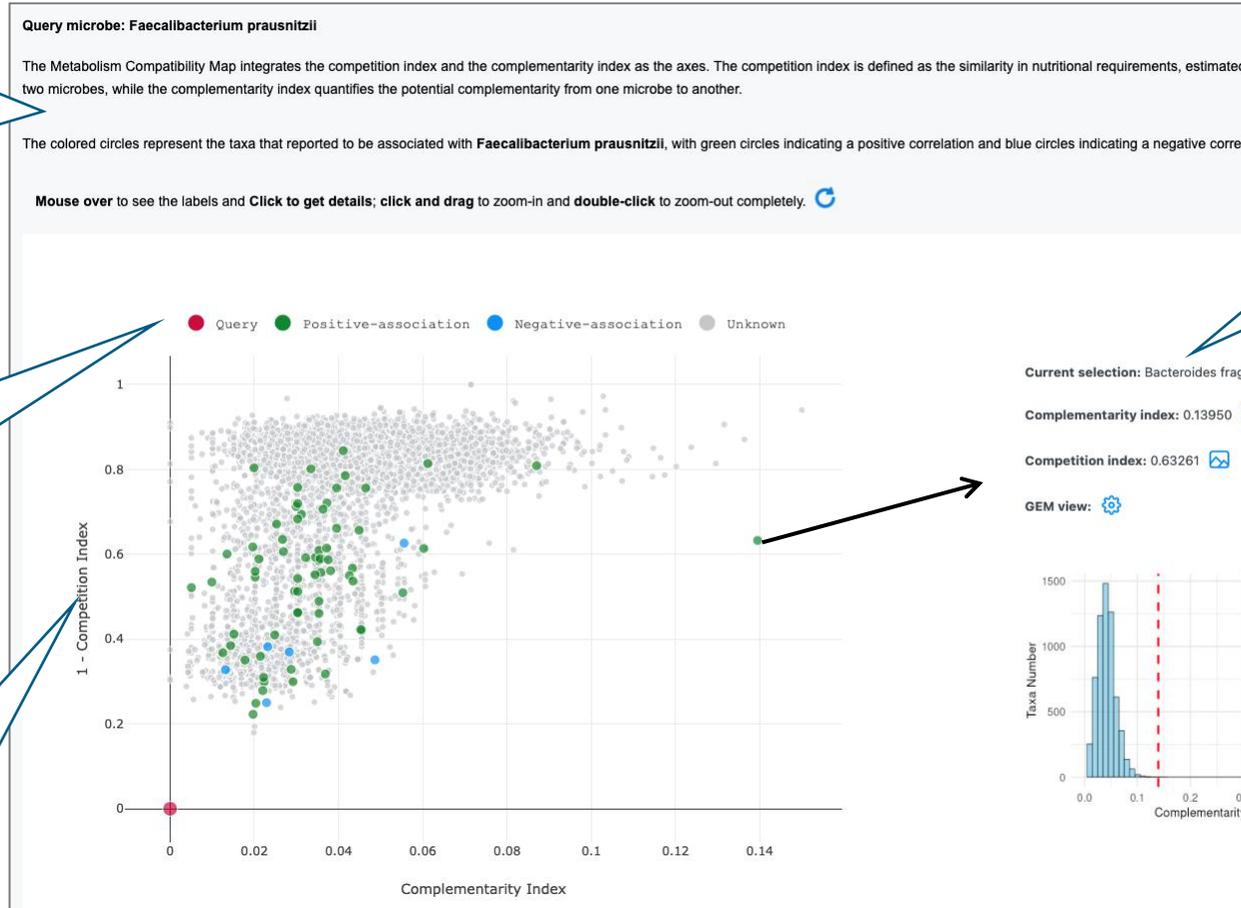
Click and Navigate to the GEM view for visual comparison

# Metabolism Compatibility Map

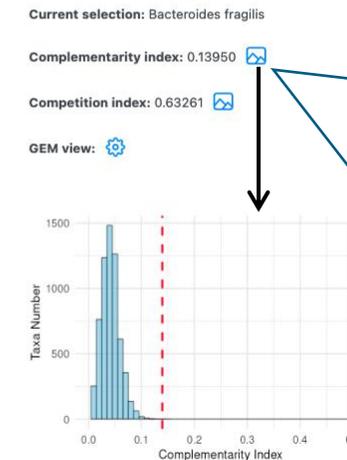
Introduction to the Metabolism Compatibility Map. More explanation refer to [Slide](#)

The colored dots are same as in the Neighborhood Map.

To ensure the x-axis and y-axis follow the same expanding trend, the y-axis uses 1-competition.



Detailed indexes are displayed here upon clicking the dots.



Click the image icon to see the rank of the selected microbe's index compared to the index calculated for all other microbes and the query microbe.

# Start from a metabolite or an enzyme

In this section, only the result pages that differ from the microbe input results are shown.

# Metabolite/Enzyme Input

Specify the query type before type in the input

For a metabolite, the name is accepted as input. For an enzyme, names at four different levels as defined by the Enzyme Commission (EC) are supported.

Microbe  Metabolite  Enzyme  Phenotype  Gene/SNP  Drug

**Please enter an item:**

**(Optional) specify a microbe:**

Examples: [#1](#) [#2](#)

Use our example for testing

An optional condition allows specifying an interested microbe based on the real biological context.

# Result Summary

Result summary using the first example of metabolite input. The result page for enzyme is the same.

The GEMs identified can metabolize the query metabolite/enzyme, providing insights into potential metabolic interactions.

## Search Result

Query Metabolite: Butyrate

Butyrate (ID: but) is found to involve in the metabolism of 9 GEMs in species *Faecalibacterium prausnitzii*

The GEM view and pathway view for higher-level taxonomy are displayed as a combination of all GEMs within the species

Click the icon to access the corresponding visualization pages. Refer to Slides 8 and 9 for the GEM view and association network.

Microbe ↑↓	Reactions ↑↓	Pathways ↑↓	Data source ↑↓	GEM View	Neighbourhood Map	Compatibility Map	Association View	Kingdom ↑↓	Phylum ↑↓
Faecalibacterium prausnitzii	BTCOAACCOAT; BUTKr	<a href="#">Butanoate metabolism</a>	Agora;CarveMe					Bacteria	Bacillota

The pathway includes the input metabolite butyrate in *Faecalibacterium prausnitzii*. Click to navigate to the pathway view

In this example, since we have specified the microbe *Faecalibacterium prausnitzii*, the result table displays information for this species. The metabolic profile represents the ensemble of GEMs within this species. If no microbe is specified, all the GEMs found will be displayed here.

The reaction includes the input metabolite butyrate in *Faecalibacterium prausnitzii*.

# Pathway View

Switching to drag mode to manually adjust the pathway layout.

Change the layout of nodes and edges.

Butanoate metabolism visualization for the selected species *Faecalibacterium prausnitzii* with related reaction highlighted.

**Butanoate metabolism in *Faecalibacterium prausnitzii***

Control Panel:

- Mode: Pan
- Color by: Pathway
- Co-factor: Hide
- Reaction node: Hide
- Background: Blue-gradient

Search metabolites:

ID	Name
<input type="checkbox"/> btd_RR	R_R_2_3_Butanediol
<input type="checkbox"/> nad	Nicotinamide adenine dinucleotic
<input type="checkbox"/> actn_R	(R)-Acetoin
<input type="checkbox"/> h	proton
<input type="checkbox"/> nadh	Nicotinamide adenine dinucleotic
<input type="checkbox"/> mal_D	D-Malate
<input type="checkbox"/> co2	Carbon dioxide
<input type="checkbox"/> pyr	Pyruvate
<input type="checkbox"/> aacoa	Acetoacetyl-CoA

Search reactions:

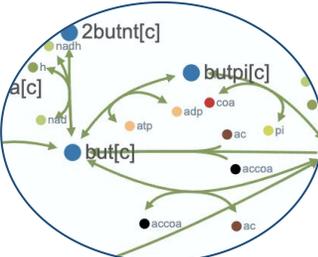
Current selection:

- [Butyryl-CoA:acetate CoA-transferase](#)
- [Butyrate kinase, reversible](#)

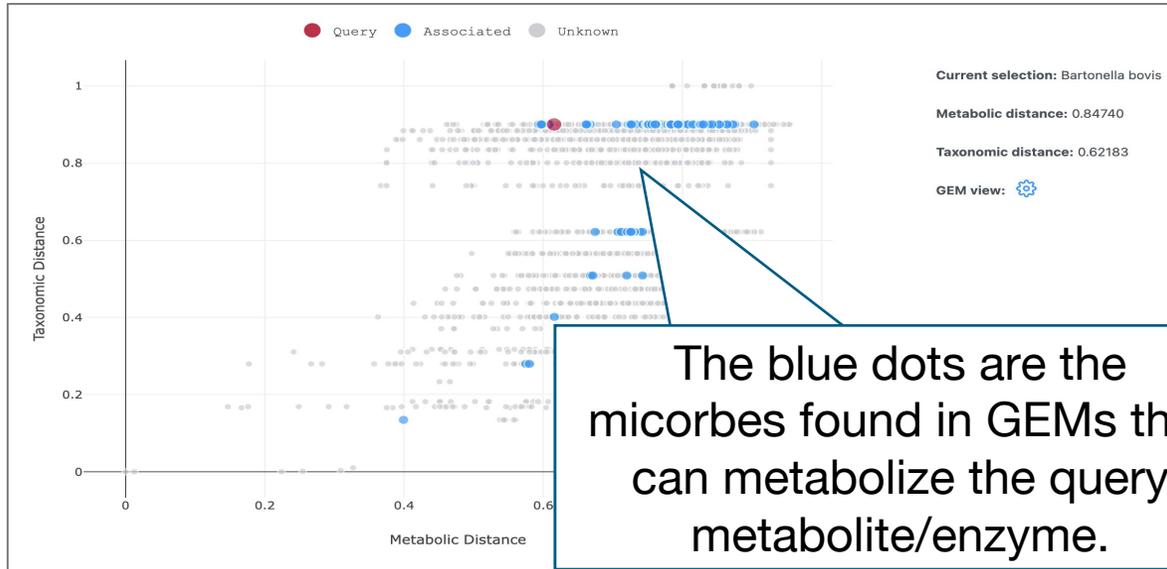
Search and highlight metabolites and reactions here

Description of the highlighted reactions

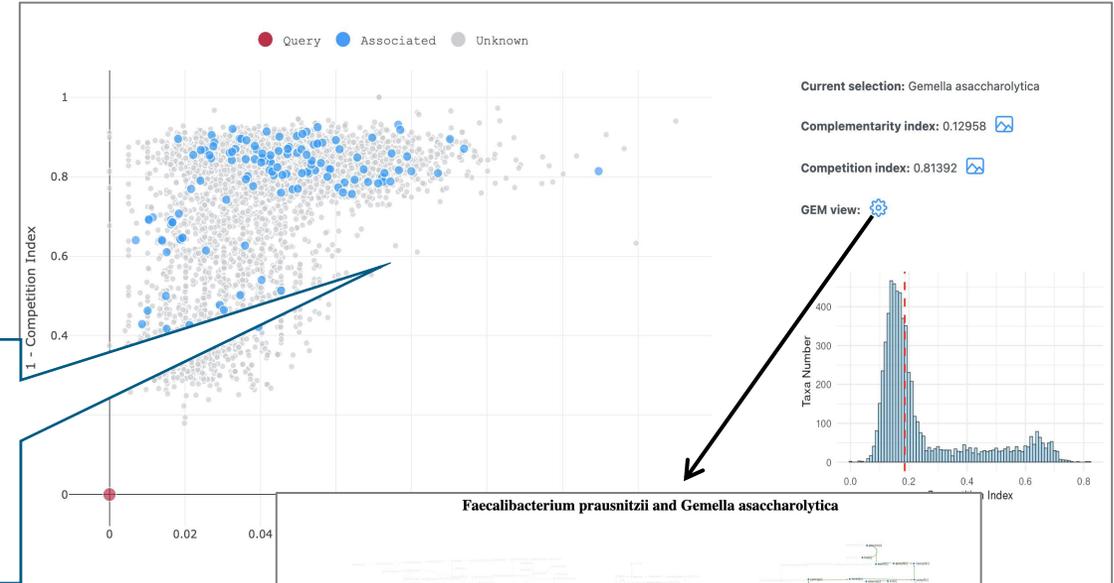
The opacity edges and nodes indicate that the metabolite and reaction are not present in the selected micorbe



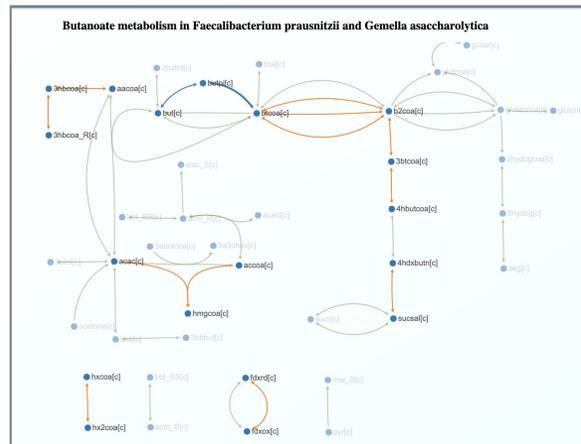
# Neighborhood Map



# Metabolism Compatibility Map



Note: The introduction of the maps is same as the for microbe query in [Slide 11](#) and [12](#). More explanations can be found in [Slide 24](#) and [25](#).



Navigate to the pathway view in GEM view by clicking the icon on the left panel

Start from:

- phenotype
- gene/snp
- drug

In this section, only the result pages that differ from the microbe input results are shown.

# Phenotype/Gene/Drug Input

Specify the query type before type in the input

For a phenotype or a drug, the name is accepted as input. For a gene or a snp, Gene symbols and SNP identifiers are acceptable.

Microbe  Metabolite  Enzyme  Phenotype  Gene/SNP  Drug

**Please enter an item:**

(Optional) specify a microbe:

Examples: #1 #2

Use our example for testing

An optional condition allows specifying an interested microbe based on the real biological context.

# Result Summary

Result summary using the first example of metabolite input. The result page for enzyme is the same.

Text summary of the associated taxa found for the input phenotype/gene/drug, Ulcerative Colitis in this example

## Search Result

Query Phenotype: Ulcerative Colitis

Ulcerative Colitis has been reported to be associated to 81 taxa at different taxonomy levels , including 56 positive

The GEM view and pathway view for higher-level taxonomy are displayed as a combination of all GEMs within the

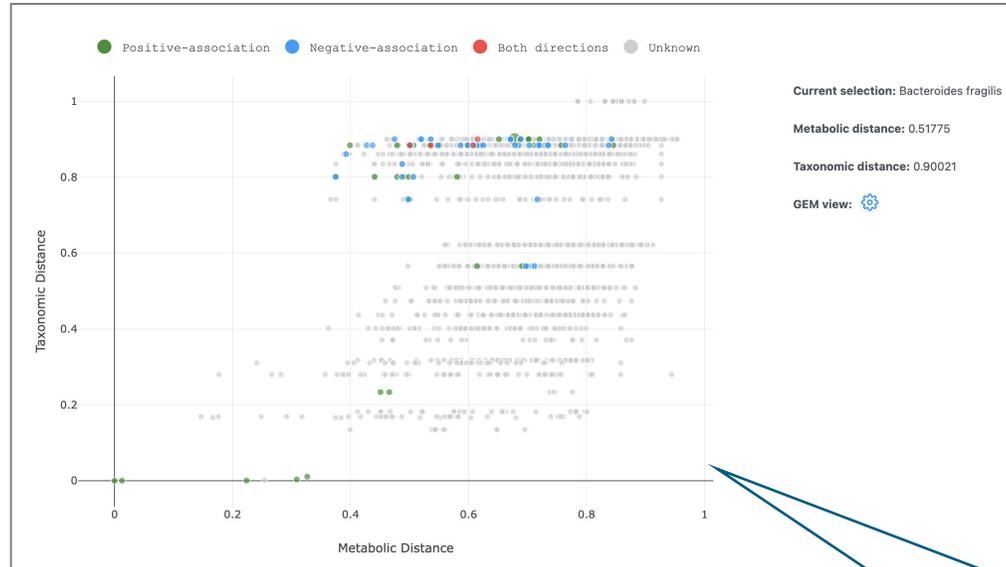
Click the icon to access the corresponding visualization pages. Refer to Slides 8 and 9 for the GEM view and association network.

Microbe ↑↓	Relation ↑↓	Host ↑↓	GEM View	Neighbourhood Map	Metabolic Map	Association View	Rank ↑↓	Reference ↑↓
Rhodococcus erythropolis	Increase	Homo Sapiens					species	<a href="#">PubMed</a>
Faecalibacterium prausnitzii	Increase	Homo Sapiens					species	<a href="#">PubMed</a>
Roseburia hominis	Increase	Homo Sapiens					species	<a href="#">PubMed</a>
[Ruminococcus] torques	Increase	Homo Sapiens					species	<a href="#">PubMed</a>
Campylobacter concisus	Increase	Homo Sapiens					species	<a href="#">PubMed</a>

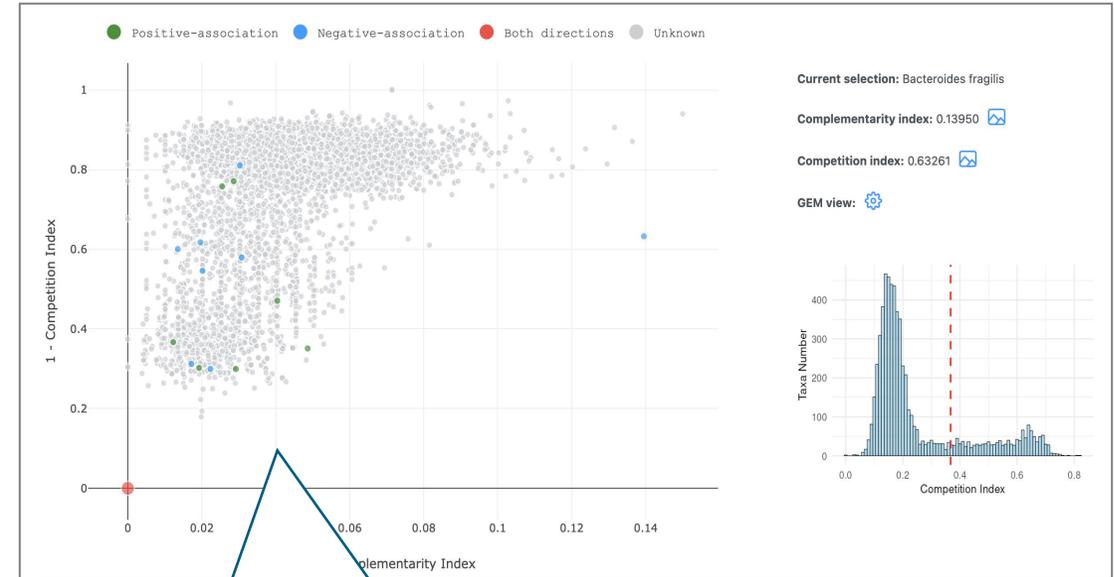
Table detailing the associated microbes, including information on host type, relation pattern, and other relevant data

Find the original study

# Neighborhood Map



# Metabolism Compatibility Map



Note: The introduction of the maps is same as the for microbe query in [Slide 11](#) and [12](#). More explanations can be found in [Slide 24](#) and [25](#).

The colored dots show the associated taxa obtained for the query phenotype/gene/drug, with green indicating a positive correlation, blue indicating a negative correlation, and red indicating both directions as found in different studies..

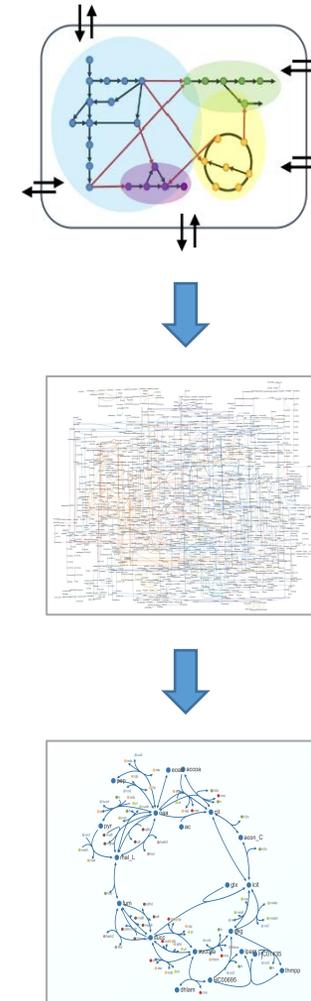


Notes

# GEMs

## Genome-scale metabolic models(GEMs):

- Computational models that represent the metabolic capabilities of an organism, encompassing the entire set of metabolic reactions taking place within an organism.
- Informative: Microbial metabolites, reactions, pathways and global metabolism
- Predictive : Metabolite requirements and production, interaction with the host and within microbial communities.



# Neighborhood Map

Neighborhood Map, display as a scatter plot, integrates metabolic distance (x-axis) and taxonomic distances (y-axis) for all taxa covered in MicrobiomeNet based on GEMs, using *E. coli* as the reference point.

- Metabolic distance:  
Determined based on the presence or absence of specific reactions in the given taxa.
- Taxonomic distances:  
Extract from a phylogenetic tree built using the NCBI Taxonomy API, which converts a list of classifications into a tree.

Both distance are normalized to a scale of 0 to 1 for comparison purposes.

# Metabolism Compatibility Map

Metabolism Compatibility Map, display as a scatter plot, integrates complementarity index (x-axis) and competition index (y-axis) for all taxa covered in MicrobiomeNet based on GEMs.

- Seed metabolite:  
The minimal group of external compounds required by a specific organism to produce all other compounds in its metabolism.
- Competition index:  
The similarity of the nutrition requirement of two microbes, denoted by the proportion of shared seed metabolites.
- Complementarity index:  
The potential for one microbe to produce the seed metabolite required by another microbe.

Both indices are asymmetrical, and the mean values are used in our tool. The original scale is maintained for comparison, as the indices are calculated within the same framework.



--END--