

MIND-A dedicated web platform to analyze microbial interaction networks

Zhenjun Hu

Research Associate Professor
Bioinformatics Program, Boston University

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Outline

- Human microbiome and associated diseases
 - Some facts
 - Role in health
 - Diseases involved
- **MIND (Microbial Interaction Network Database)** platform
 - Mission and goals
 - Challenges
 - Implementation and status
 - Future development

Human microbiome and associated diseases - some facts

- **Human microbiome:** microbial communities in the human body, mainly of bacteria, but also include protozoa, archaea, viruses, and fungi.
 - 10 fold of the H.sapiens cells, ~350 trillion in total
 - Gut microbiota is the most abundant microbial with ~1000 species, >90% are Firmicutes and Bacteroidetes
 - Human microbiome is personal
 - Variability factors: host genetics, feeding habits, life style, and medicine etc.
 - The recent development is contributed mainly by metagenomics and metatranscriptomic analysis.

Human microbiome and associated diseases - role in health

- The relationship between host and microbiota is **symbiotic** and **mutualistic**.
 - The host provides a protected and nutrient-rich environment
 - The microbiota enhance functions in digestion, immunity, and neuronal development etc.
 - Changes in human microbiota have profound impacts on health and may predispose to different immunological and pathological conditions
 - Absence of gut microbiota leads to increased bone mass in mice
 - Microbiota also impacts the permeability of the intestinal barrier, therefore effects the drug delivery
 -

Human microbiome and associated diseases (Cont.)

Dysbiosis of microbiota (especially in the gut) predisposes to many different diseases

- **Intestinal diseases:** including Crohn's disease (CD) and ulcerative colitis, colorectal cancer, irritable bowel syndrome etc.
- **Metabolic disorders:** obesity, diabetes, or non-alcoholic fatty liver disease etc.
- **Gastric diseases:** chronic atrophic gastritis, stomach ulcers → gastric cancer or precancerous conditions
- **Liver diseases:** nonalcoholic steatohepatitis, liver cirrhosis
- **Cardiovascular diseases:** atherosclerosis, heart attack etc.
- **Neurodegenerative diseases:** Alzheimer's disease, autism, Parkinson's disease etc.

MIND Platform – mission and goals

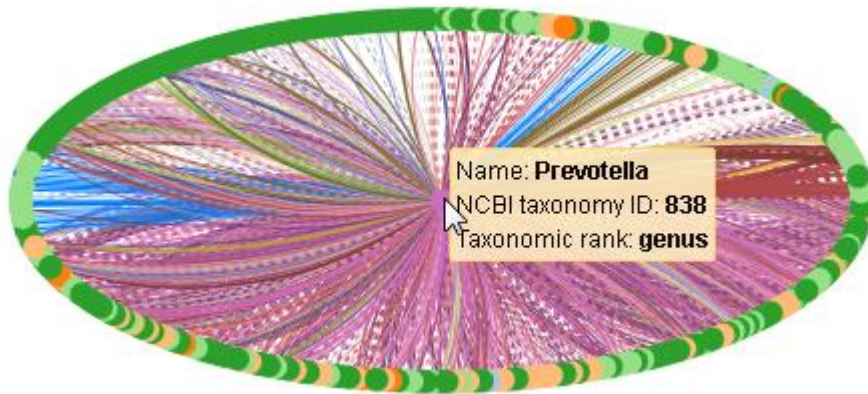
Despite the rapid development of microbiome studies with some successful studies, majority of them however failed to identify distinct biomarkers. From this perspective, we propose to use a network approach to:

- find diagnostic and prognostic patterns,
- distinguishing correlation from causation,
- determine the mechanisms by which microbial cells interact with one another and with host cells,
- developing a predictive understanding of dynamical changes under specified perturbations

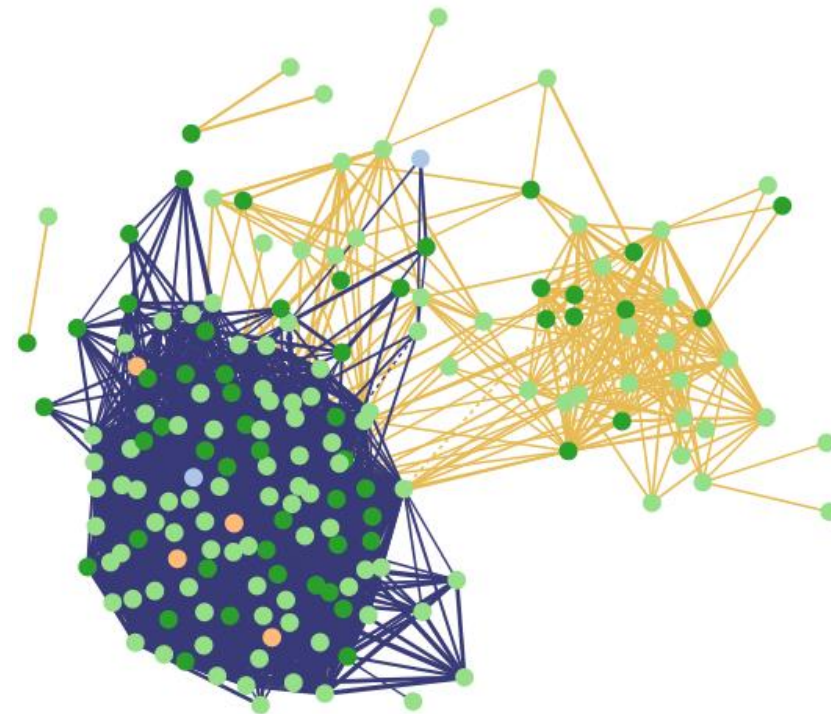
MIND platform is available at: <http://microbialnet.org/>

MIND Platform – Challenges in the analysis of microbial networks

- Low resolution and mixed taxonomic level make the comparison of the networks, especially cross-study comparisons, difficult:



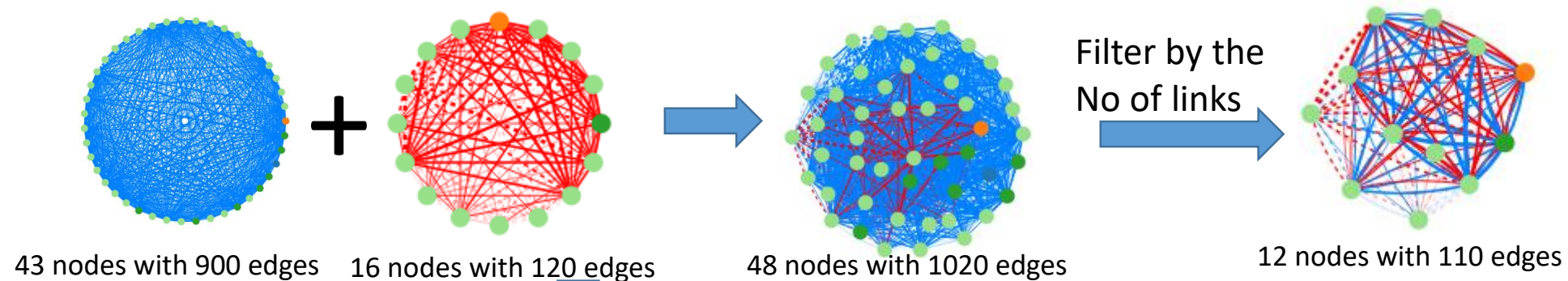
Microbes interacting with Prevotella (Oct. 10th, 2018)



Comparison of the healthy gut microbial network from two different studies

MIND Platform – Challenges in the analysis of microbial networks (cont.)

2. Inconsistency cross different studies:



[BMC Infect Dis.](#) 2013 Oct 16;13:480. doi: 10.1186/1471-2334-13-480.

Vaginal microbiome in women from Greenland assessed by microscopy and quantitative PCR.

[Datcu R](#), [Gesink D](#), [Mulvad G](#), [Montgomery-Andersen R](#), [Rink E](#), [Koch A](#), [Ahrens P](#), [Jensen JS](#)¹.

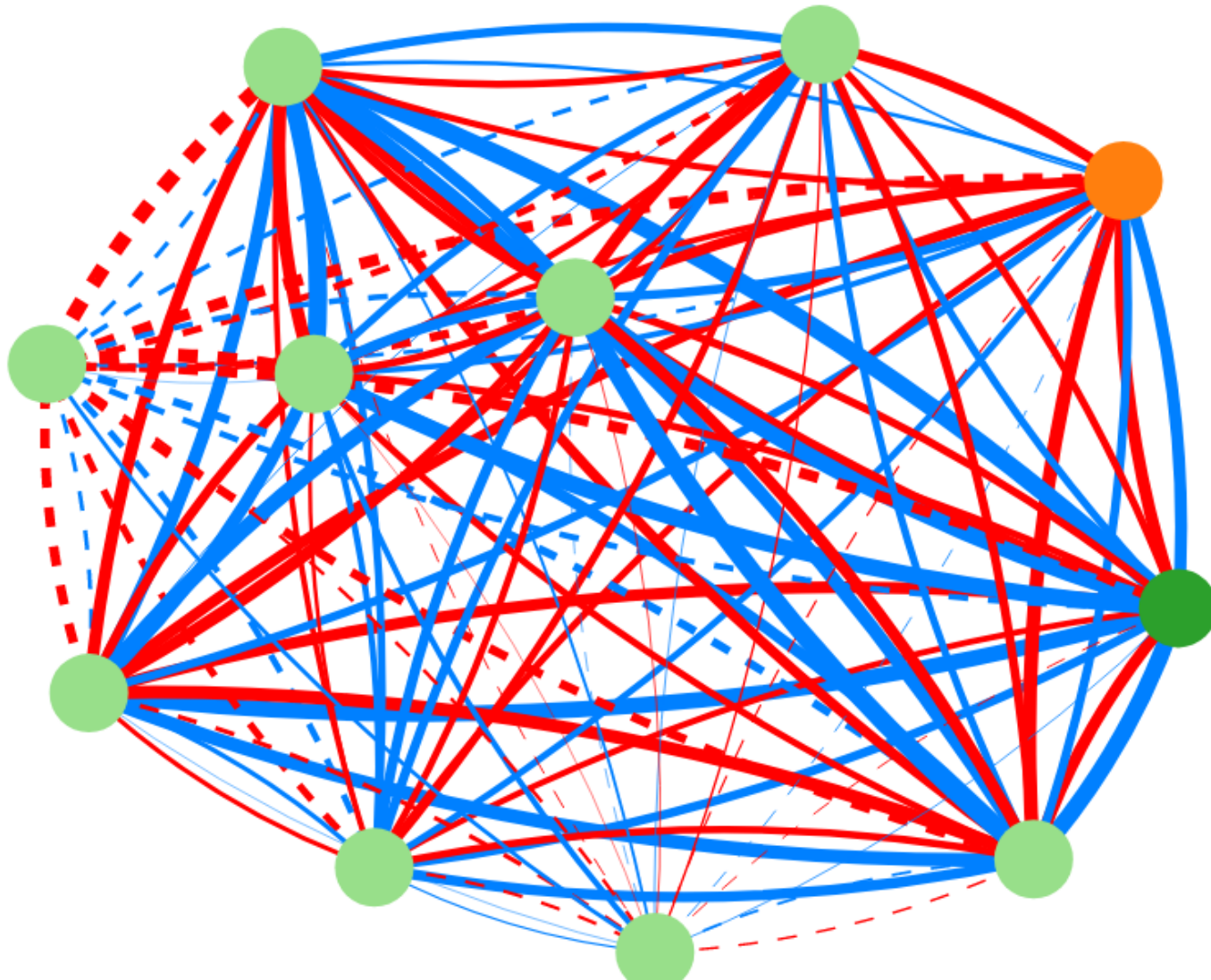
[PLoS One](#). 2012;7(6):e37818. doi: 10.1371/journal.pone.0037818. Epub 2012 Jun 18.

Bacterial communities in women with bacterial vaginosis: high resolution phylogenetic analyses reveal relationships of microbiota to clinical criteria.

[Srinivasan S](#)¹, [Hoffman NG](#), [Morgan MT](#), [Matsen FA](#), [Fiedler TL](#), [Hall RW](#), [Ross FJ](#), [McCoy CO](#), [Bumgarner R](#), [Marrazzo JM](#), [Fredricks](#)

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MIND Platform – Challenges in the analysis of microbial networks (cont.)



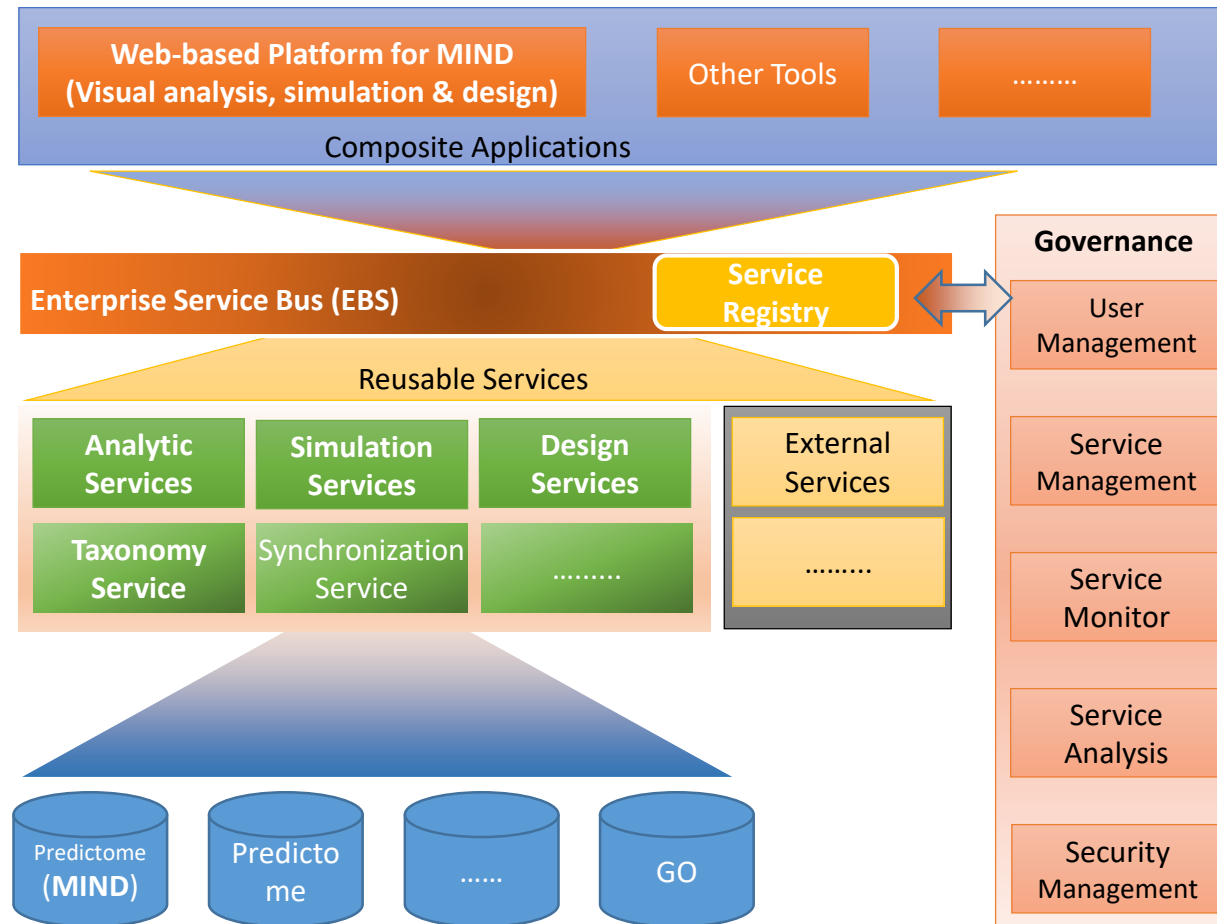
MIND Platform – Challenges in the analysis of microbial networks (cont.)

We developed two parallel projects to address the challenges

- We developed a set of functions in MIND web platform to address the characteristic features of microbial networks
- In addition to the direct curation of those networks available in the literature, we performed a deep analyses of the existing algorithms and developed MIND pipeline with optimized parameters to extract the correlation networks either from 16 sRNA, or from OTU (operational taxonomic unit).

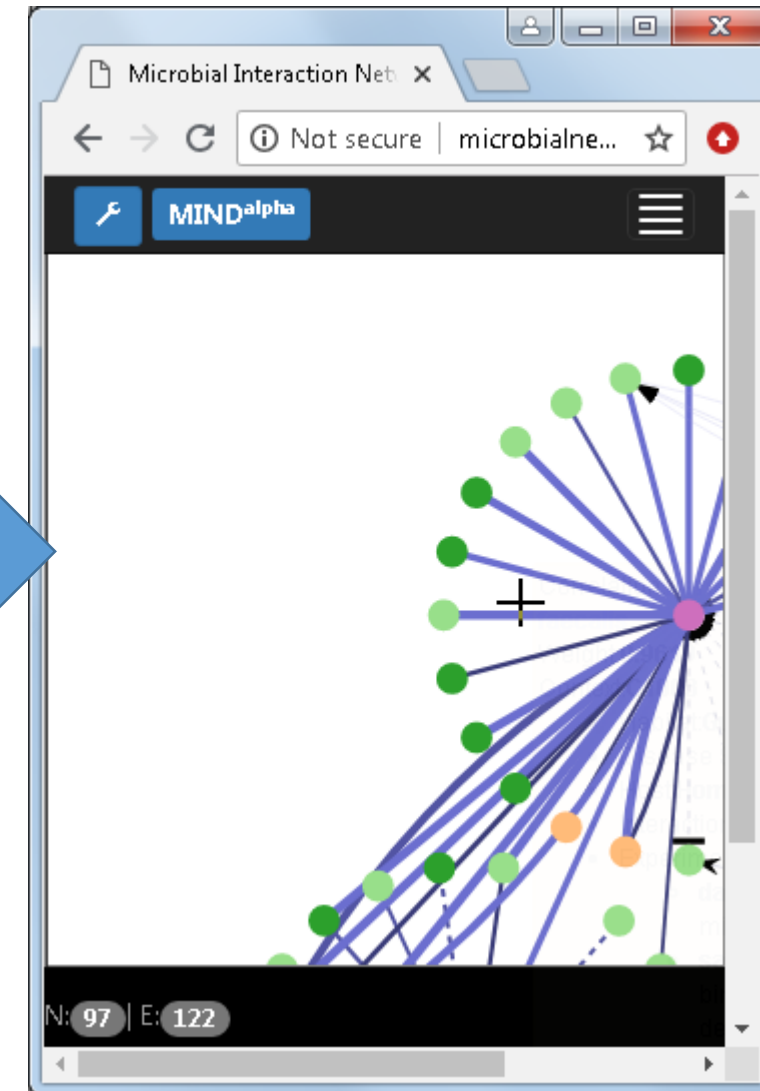
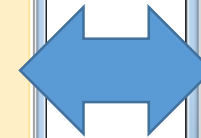
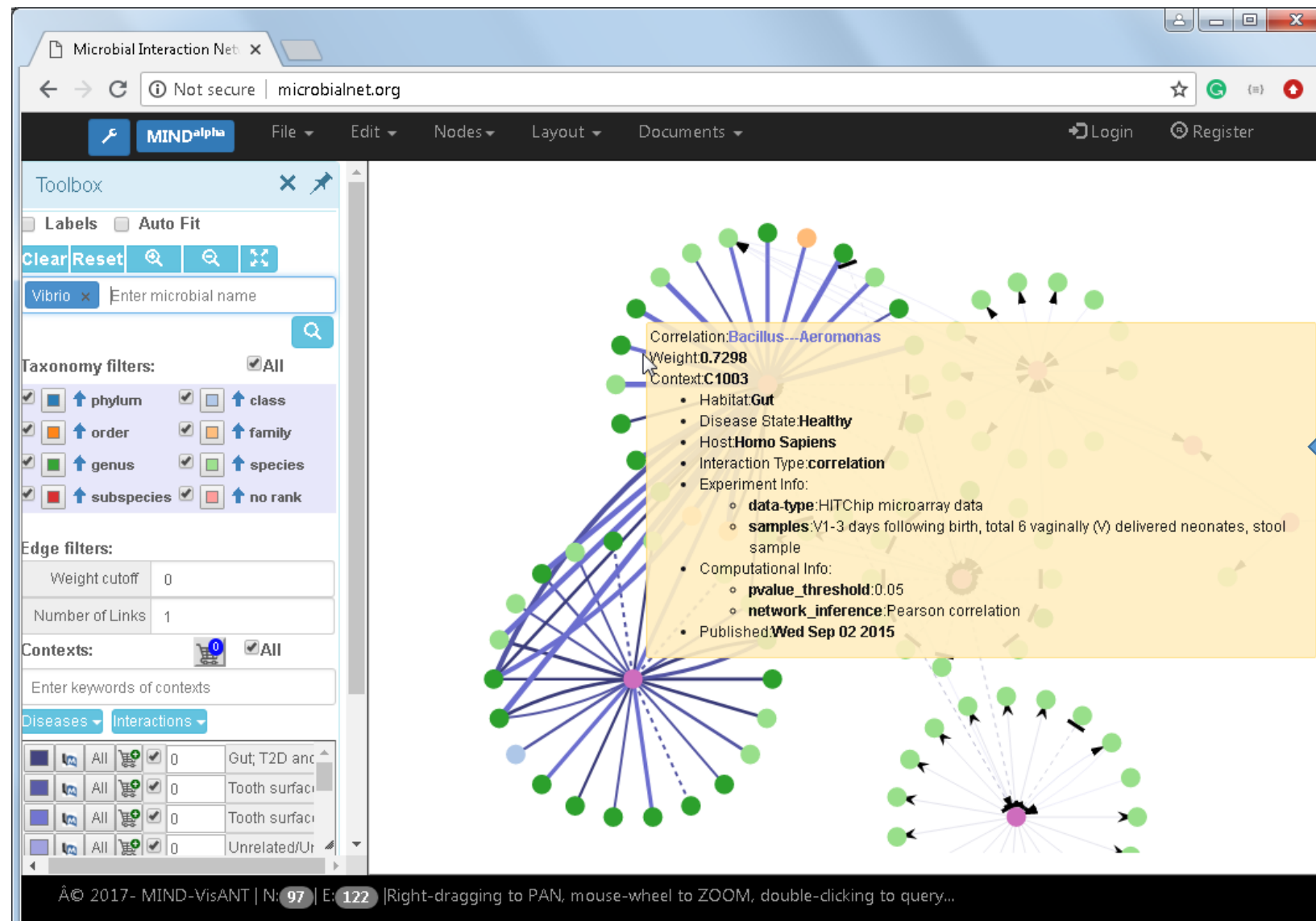
MIND Platform – Implementation and status

System architecture:



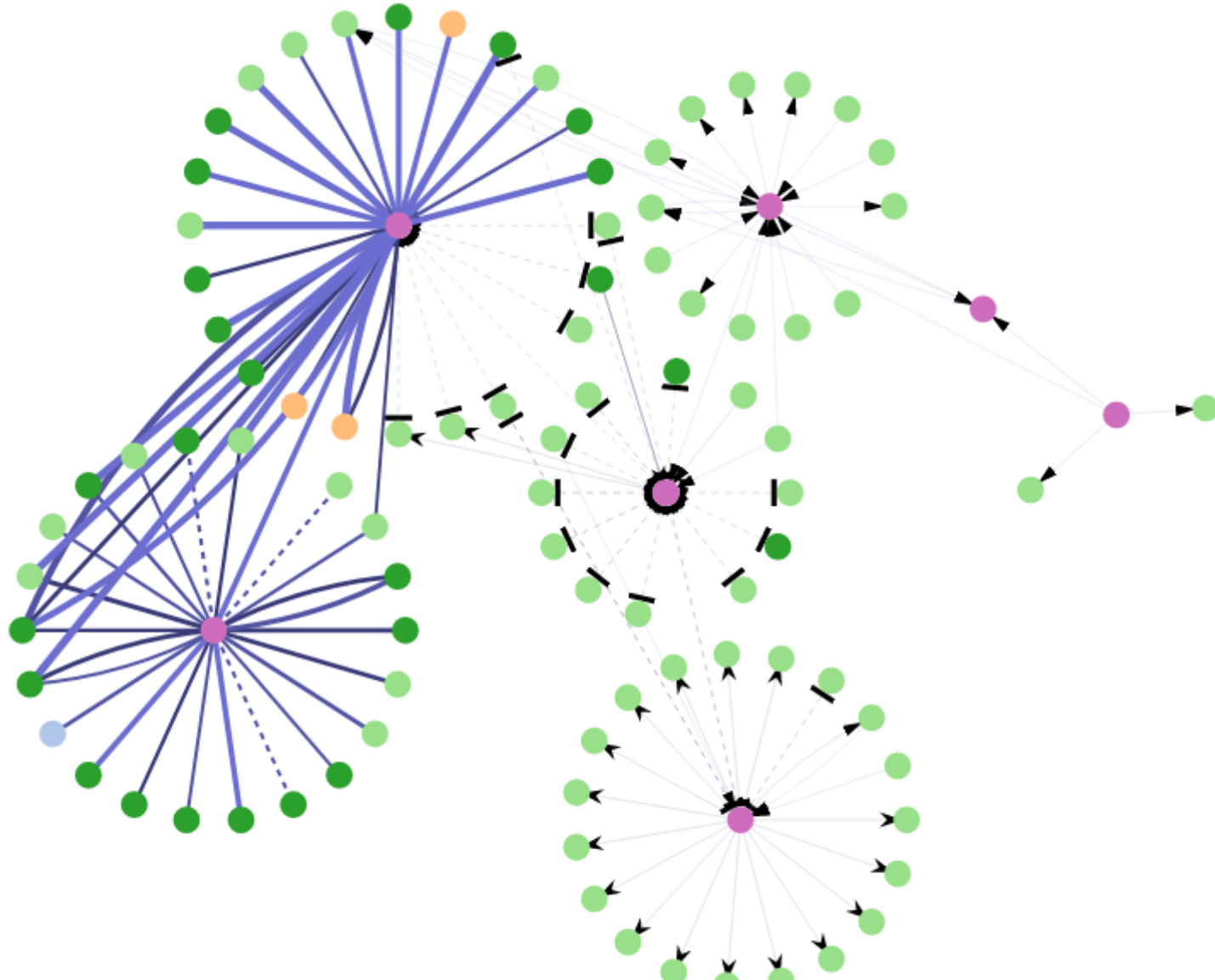
MIND Platform – Implementation and status (cont.)

Overview: designed as a single page application with responsive UI



MIND Platform – Implementation and status (cont.)

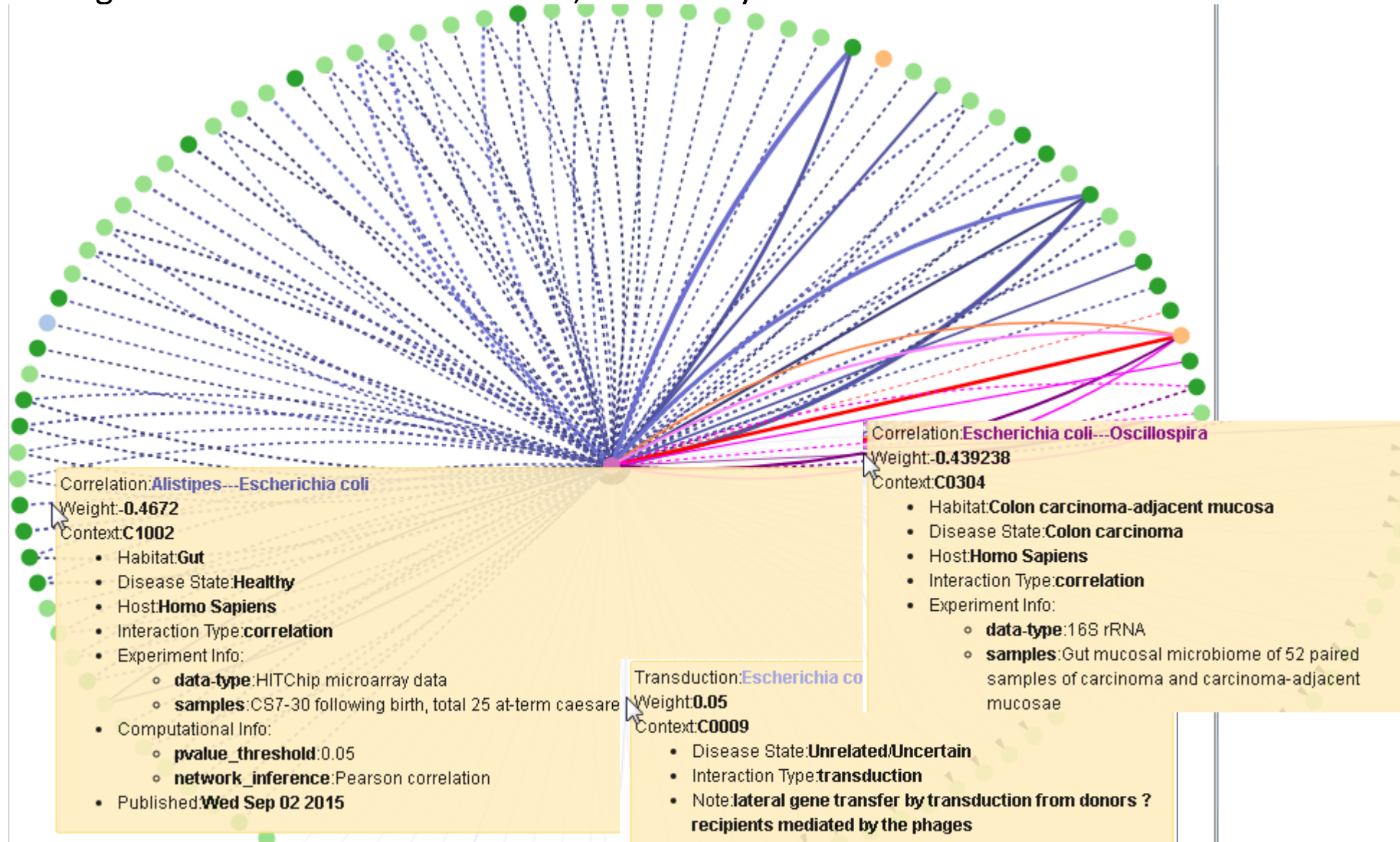
Exploratory navigation starting with the microbes of interest:



MIND Platform – Implementation and status (cont.)

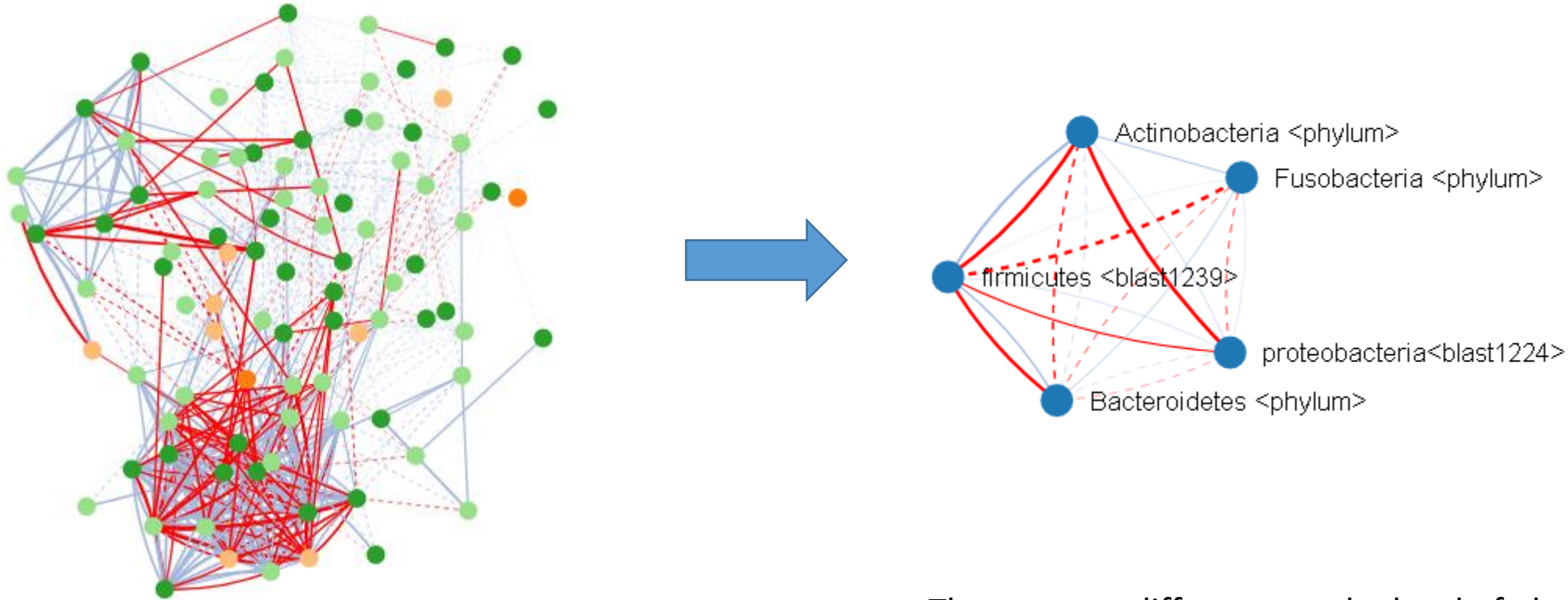
Exploratory navigation starting with the microbes of interest, case study with *Escherichia coli*

- *E. Coli* exists in healthy sample
- *E. Coli* also appears in the sample of colon cancer
- However, they have totally different interacting components



MIND Platform – Implementation and status (cont.)

Comparative analysis: among **the same study** (red line for the colon cancer, light blue for normal)

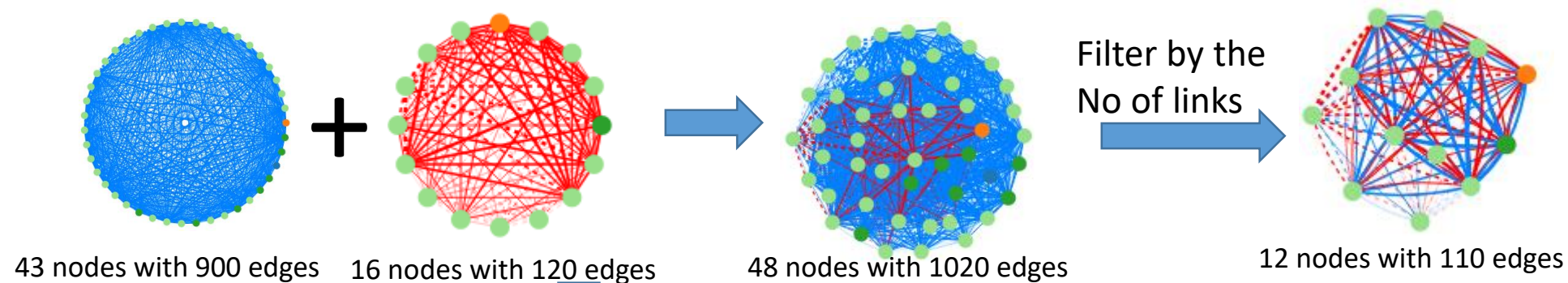


Reduced composition and diversity, as well as their interactions in cancer samples

There are no difference at the level of phylum

MIND Platform – Implementation and status (cont.)

Comparative analysis: cross **different studies**



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Vaginal microbiome in women from Greenland assessed by microscopy and quantitative PCR.

[Datcu R, Gesink D, Mulvad G, Montgomery-Andersen R, Rink E, Koch A, Ahrens P, Jensen JS¹.](#)

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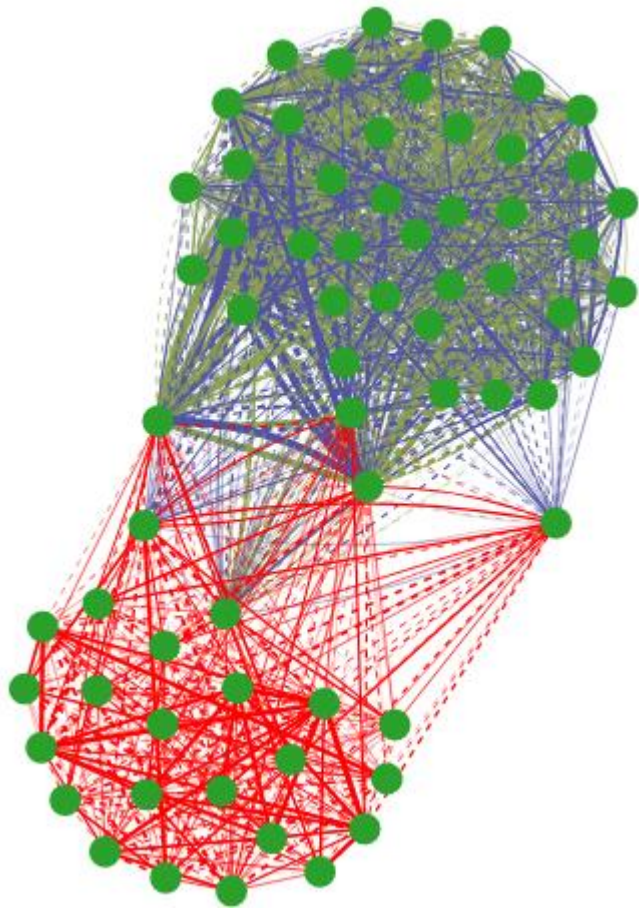
Bacterial communities in women with bacterial vaginosis: high resolution phylogenetic analyses reveal relationships of microbiota to clinical criteria.

[Srinivasan S¹, Hoffman NG, Morgan MT, Matsen FA, Fiedler TL, Hall RW, Ross FJ, McCoy CO, Bumgarner R, Marrazzo JM, Fredricks](#)

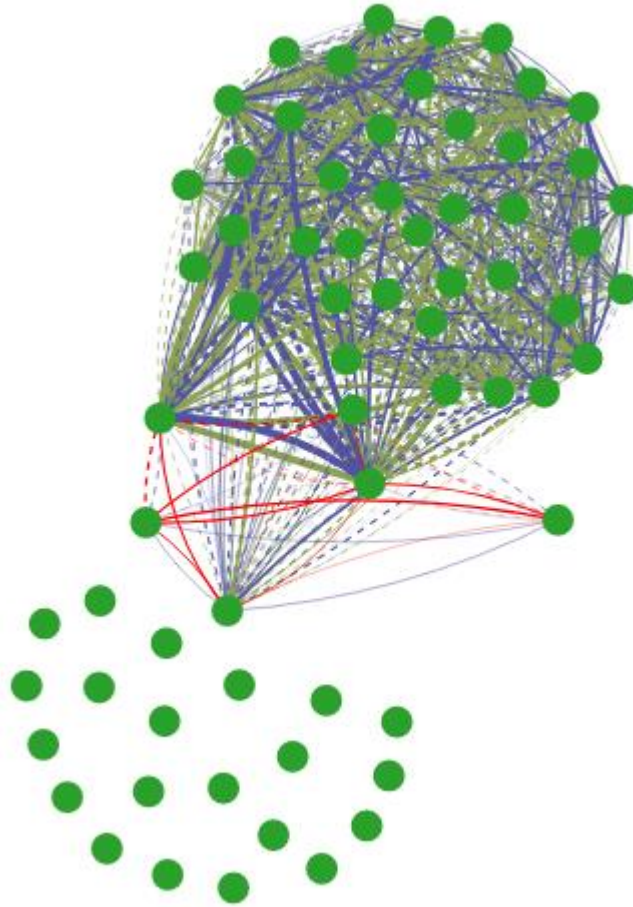
[DN](#)

MIND Platform – Implementation and status (cont.)

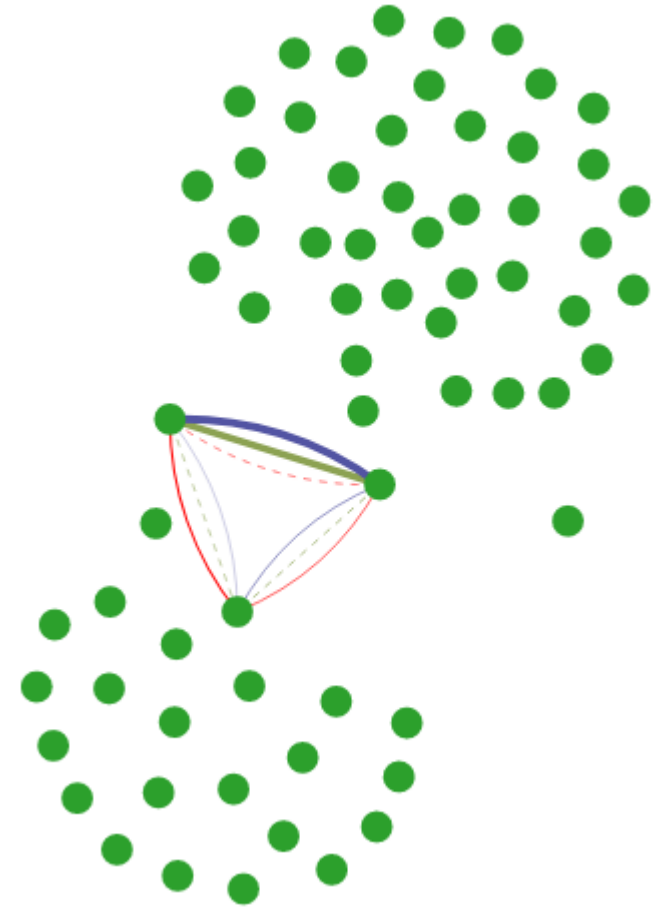
Comparative analysis: **cross body sites** (Red: gut, Light blue: saliva, Green: throat):



- habitat-specific modularity
- A lot overlap of the network in throat and saliva



- Filter out interactions only appear in **one** body site
- Network in gut is very different

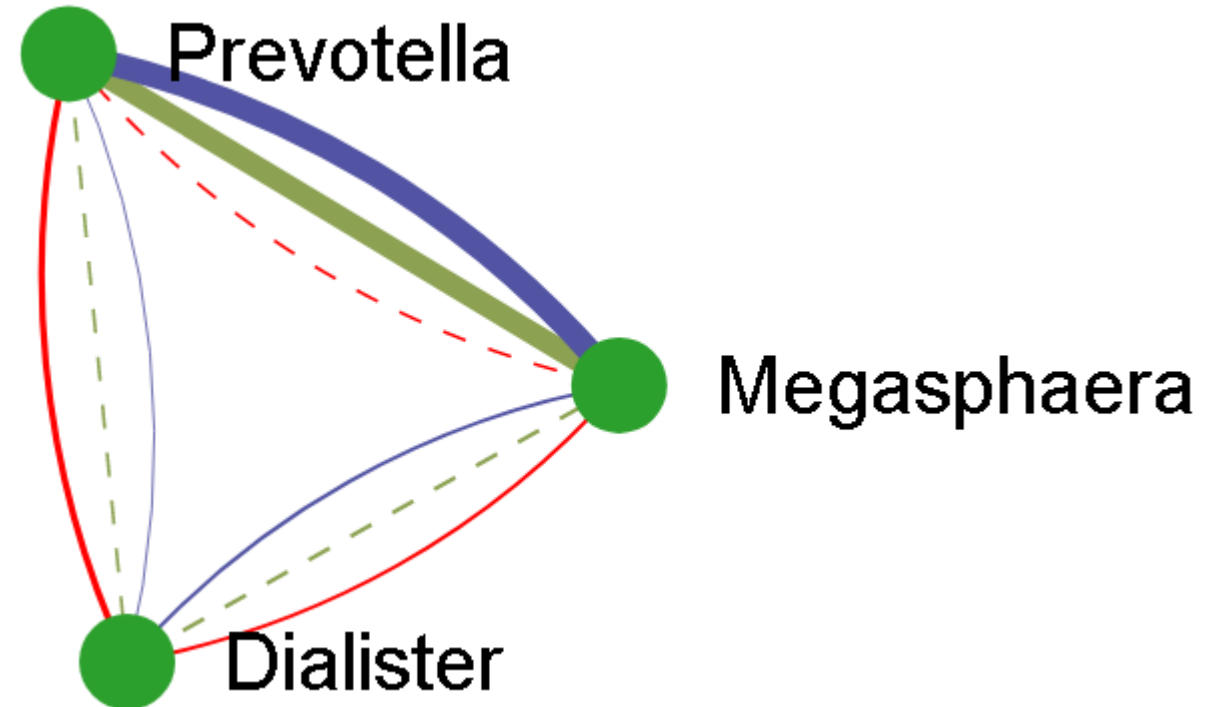


- Filter out interactions only appear in **two** body site
- Three genus are fully connected

MIND Platform – Implementation and status (cont.)

Comparative analysis: **cross body sites** (Red: gut. Light blue: saliva, Green: throat):

- *Prevotella*
 - well-known as a human pathogen for creating periodontal and tooth problems, although it also appear popular in healthy mouth
 - About 20 identified species of *Prevotella* are known to cause infection
 - Elevated *Prevotella* has been reported in CVD and T2D and Hypertension
 - Also popular in stomach
- *Dialister*
 - pathogenic potential in various sites of the body including the lung, brain, and dental root canals
- *Megasphaera*
 - a major group within the oral habitat, they have never been isolated in cultivable form to date



Oral microbial transit occurs at low levels in the normal adult microbiome , although it is clearly important during founding of the microbiome in infancy and in extreme cases such as illness

MIND Platform – Implementation and status (cont.)

Data organization and flexible format for exchange

- Microbial interactions are organized by the context that contains a list of flexible information regarding the network
- Generic JSON format for data submission and exchange









```
{
  "contexts": [
    {
      "host": "Homo Sapiens",
      "interaction_type": "correlation",
      "condition": "Healthy",
      "location": "Gut",
      "description": "Controls from a Fecal Microbiome Transplant experiment, stool sample",
      "publication": {
        "authors": [
          {
            "name": "Dileep Kishore",
            "email": "dkishore@bu.edu"
          }
        ],
        "pubmed_id": "0123",
        "date": "2018-08-22"
      },
      "computational_metadata": {
        "denoising": "deblur",
        "interaction_threshold": 0.3,
        "network_inference": "SparCC",
        "pvalue_correction": "fdr_bh",
        "pvalue_threshold": 0.05,
        "taxonomy_db": "greengenes",
        "directionality": "undirected"
      },
      "experimental_metadata": {
        "data-type": "16S rRNA",
        "platform": "illumina",
        "region": "V4"
      }
    }
  ],
  "links": [ ],
  "nodes": [ ]
}
```

MIND Platform – Implementation and status (cont.)

Flexible filters to facilitate the comparative analyses

- Filter or level up nodes across different taxonomic ranks

Taxonomy filters: ☒ All


<input checked="" type="checkbox"/>  ↑ phylum	<input checked="" type="checkbox"/>  ↑ class
<input checked="" type="checkbox"/>  ↑ order	<input checked="" type="checkbox"/>  ↑ family
<input checked="" type="checkbox"/>  ↑ genus	<input checked="" type="checkbox"/>  ↑ species
<input checked="" type="checkbox"/>  ↑ subspecies	<input checked="" type="checkbox"/>  ↑ no rank

- Filter interactions based on no of interactions and global weight cut-offs

Edge filters:









Weight cutoff	0
Number of Links	1

- organize the contexts using carts


Contexts:  ☒ All

Enter keywords of contexts

Normal





















		All			0	Colon mucos
		All			0	Colon carcin

- Filter networks with contexts and context-specific weight cut-offs

Contexts:  ☒ All

Enter keywords of contexts



Normal

		All			0	Gut; T2D and
		All			0	Tooth surfac
		All			0	Tooth surfac
		All			0	Unrelated/Ur
		All			0	Colon mucos

- Filter contexts with predefined filters

Normal

Diseases

		All	<div>metabolic influence</div> <div>binding</div> <div>transduction</div> <div>correlation</div> <div>metabolic complementarity in</div> <div>metabolic competition index</div>
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		All
		All
		All
		All
		All
		All
		All

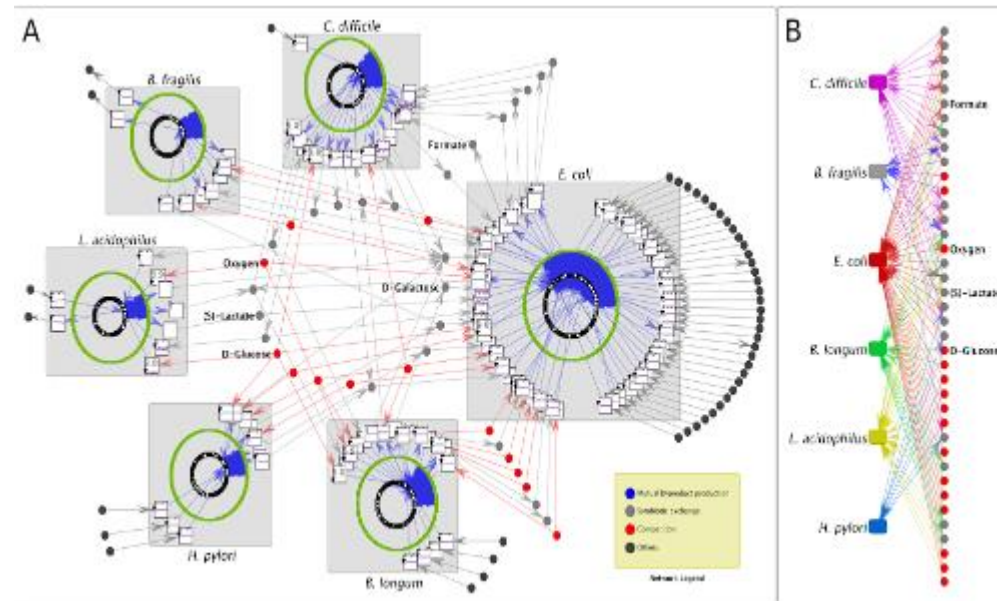
Normal

All
T2D and non-diabetic control
Healthy
Unrelated/Uncertain
Normal
Colon adenoma
Colon carcinoma
Axillary odour
Prehypertension
Hypertension
Mixed
Bacterial vaginosis

MIND Platform – Implementation and status (cont.)

Future development

- Introduce more types of interactions to make it easier to infer causal microbial interaction
- Development algorithms for versatile analyses such as topological analysis, community detection etc.
- Improve the user-friendliness of the platform, provide functions such as undo/redo etc.
- Facilitate the data submission
- Implement the metagraph technology to fully integrate with VisANT-Predictome system for multi-scale/cross-scale analyses



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