Multi-Stage Probabilistic Bipartite Graph Algorithm - Effect of Herbal Medicines on the Gut Ecosystem

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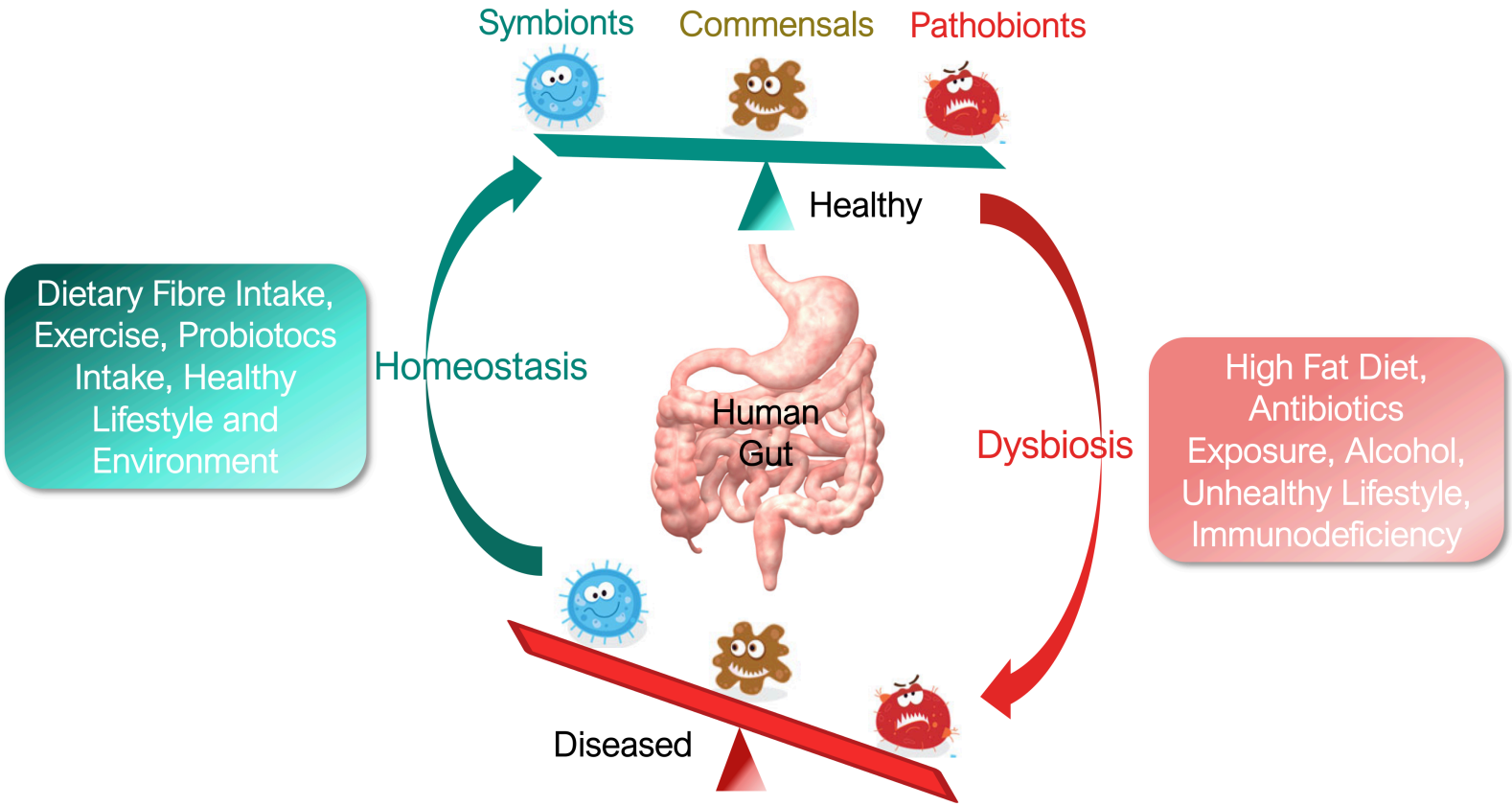
Presenter: Suganya Chandrababu

Straightforward Overview

- Purpose/value of the study
- Effect of Herbs on the Gut Ecosystem
- Our Contribution
- Multi-stage Graph Probabilistic Algorithm
- Dataset Used
- Results and Discussion
- Conclusion
- Limitations
- Future Work

Why do we care?



- Such imbalance could result in intestinal and extra-intestinal disorders, including inflammatory bowel disease (IBD), diabetes mellitus (DM), obesity, etc.

Pharmacological Effects of Natural Products

Role of Gut Microbiota in the Pharmacological Effects of Natural Products

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Chemoprevention in Gastrointestinal Physiology and Disease. Natural products and microbiome

Allen K. Greiner,[1] Rao V. L. Papineni,[1,2,3] and Shahid Umar[1]

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Submitted in final form 25 April 2014

Berberine Regulates Treg/Th17 Balance to Treat Ulcerative Colitis Through Modulating the Gut Microbiota in the Colon

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REVIEWS: CURRENT TOPICS

Anthocyanins as inflammatory modulators and the role of the gut microbiota

Carina Almeida Morais, Veridiana Vera de Rosso, Débora Estadella, Luciana Pellegrini Pisani*

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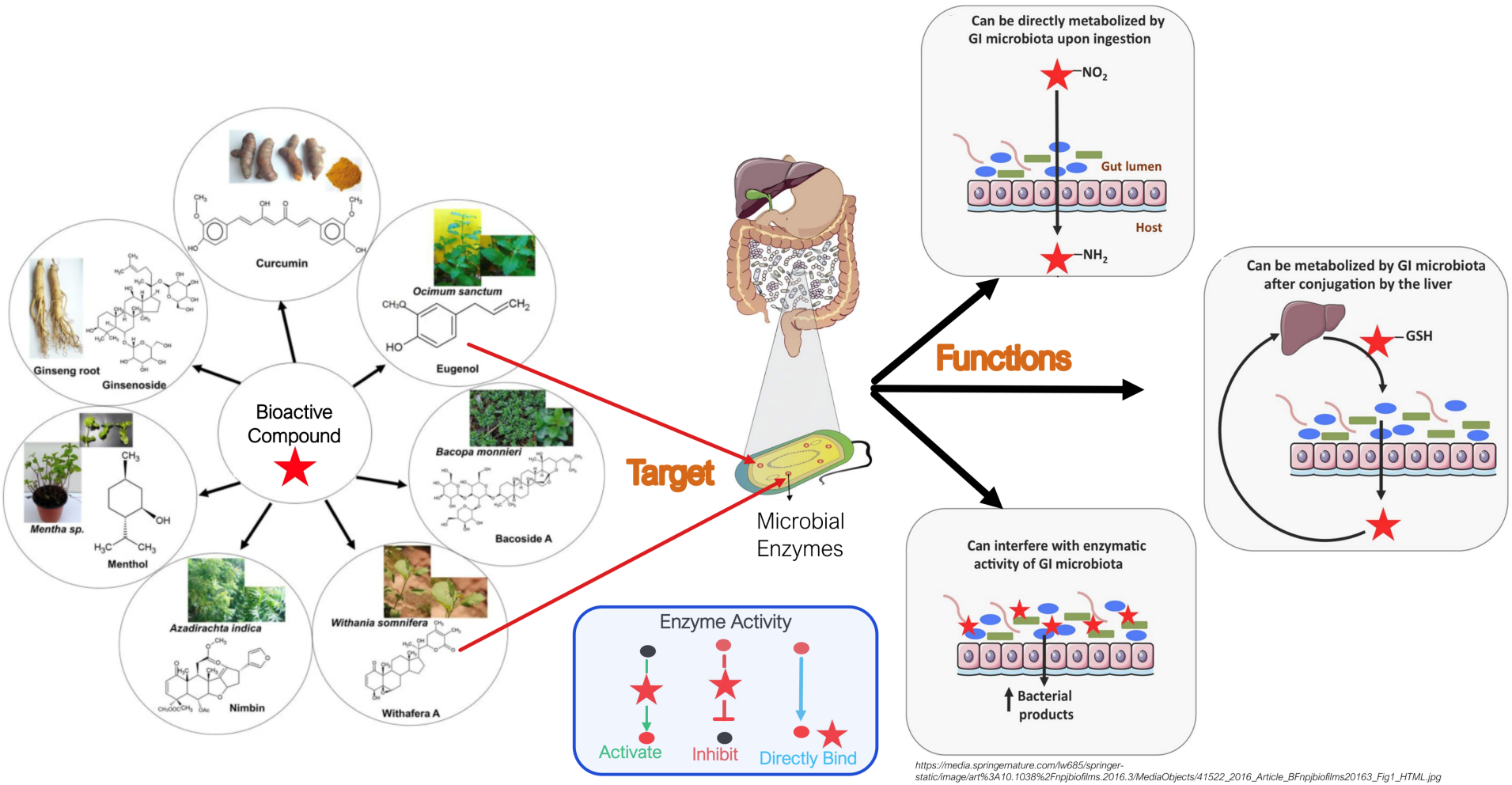
Volume 216, 24 April 2018, Pages 47-56

Ginseng polysaccharides enhanced ginsenoside Rb1 and microbial metabolites exposure through enhancing intestinal absorption and affecting gut microbial metabolism

Herbs Modulate Gut Bacterial Metabolism



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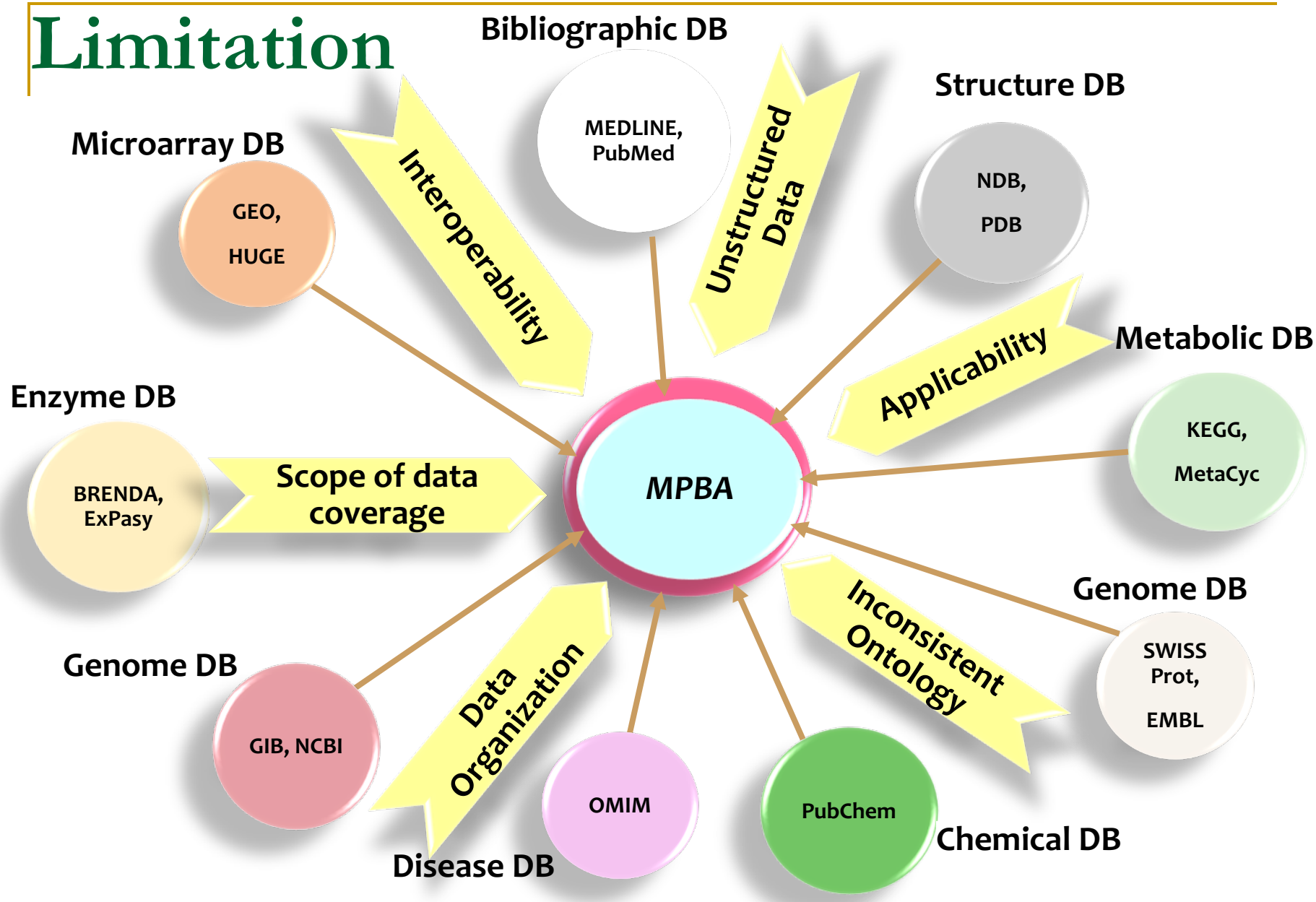
Limitation


Bibliographic DB
MEDLINE, PubMed
Unstructured Data
Structure DB
NDB, PDB
Microarray DB
GEO, HUGE
Interoperability
Applicability
Metabolic DB
KEGG, MetaCyc
Enzyme DB
BRENDA, ExPasy
Scope of data coverage
MPBA
Genome DB
SWISS Prot, EMBL
Inconsistent Ontology
Genome DB
GIB, NCBI
Data Organization
OMIM
PubChem
Chemical DB
Disease DB

Why Hear the Talk?

To

- understand a comprehensive method that integrates knowledge from multiple sources.
- know how to characterize the microbial dysbiosis.
- evaluate the pharmacological value of herbal medicine.
- learn how and which herbs can modulate the gut microbial functions.

What is our contribution?

We

- provide a ***systems-level characterization*** of the effects of the small molecules in herbs on the bacterial genes and metabolic pathways.

- propose a ***computational network-based approach-*** the **M**ulti-stage **P**robabilistic **B**ipartite graph **A**lgorithm (**MPBA**), which integrates the complex heterogeneous metabolism/pathway data from herbs to gut bacteria.

Background Work

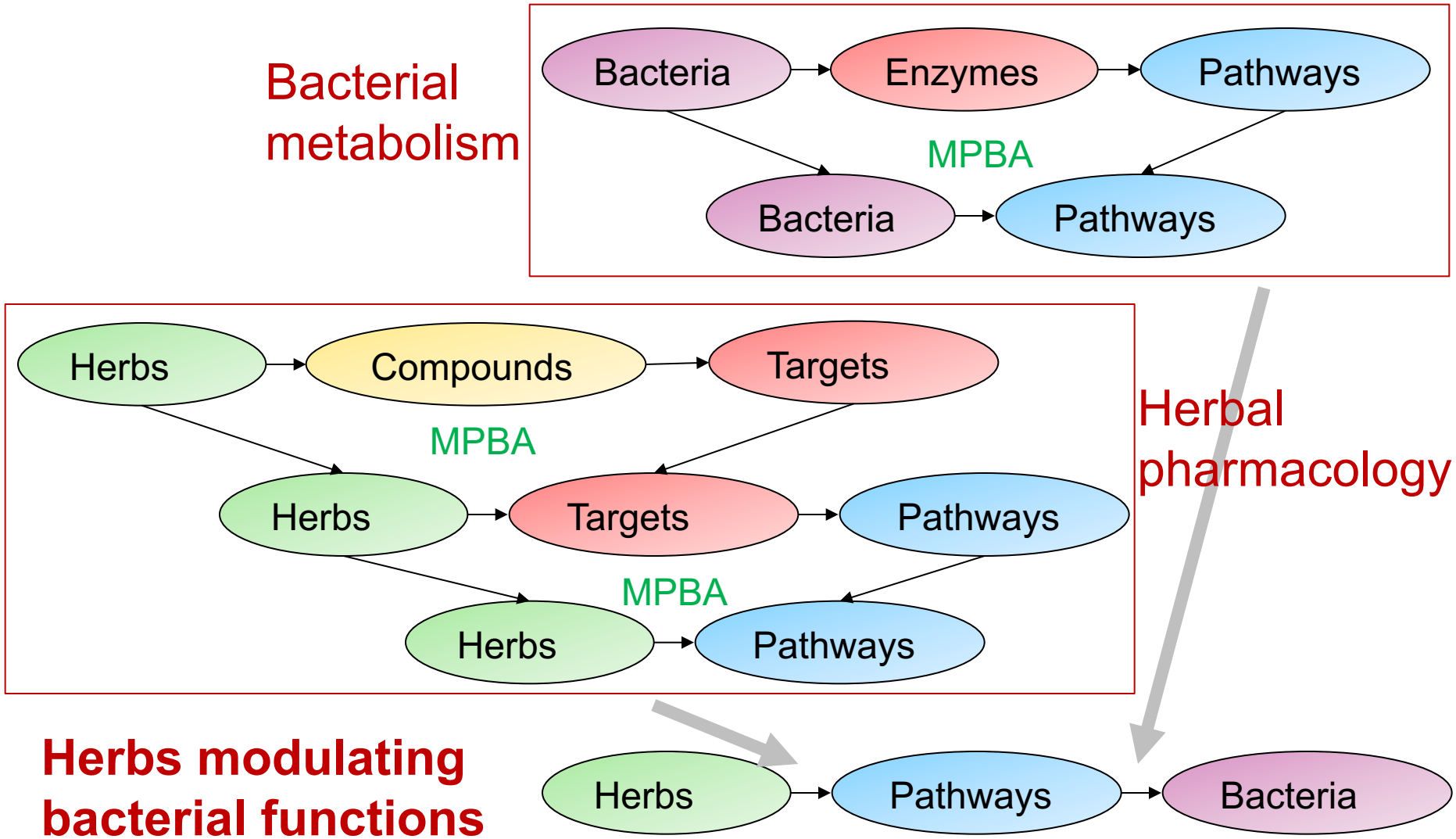
- **The human colon modulates of gut immune function**, protects the host against pathogens and diseases. [D. C. Savage, et al., 1997, R. E. Ley, et al., 2010]

- **Variations in products of bacterial metabolism** have been implicated as a causative agent in serious diseases, including cancer (example: *Helicobacter pylori*). [Flint, Harry J., et al., 2012]

- **Herbal medicine are useful in the treatment of dysbiosis** and serve as a multi-targeting complementary/alternative medicine/probiotic in the management of colon health, [M. Sałaga, et al., 2014, F. Ke, et al., 2012]

Multi-Stage Probabilistic Bipartite Graph Algorithm

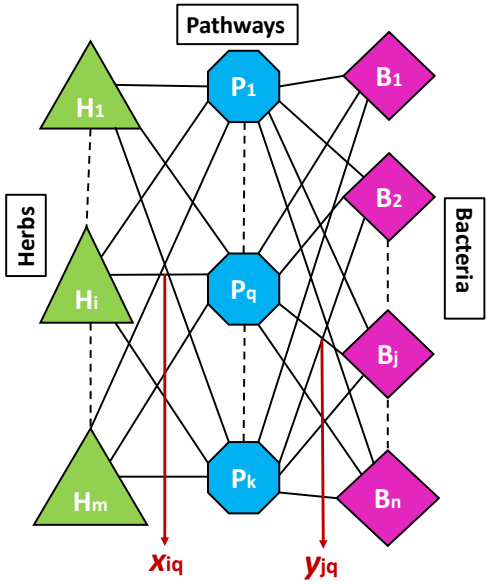
Our Prediction Model

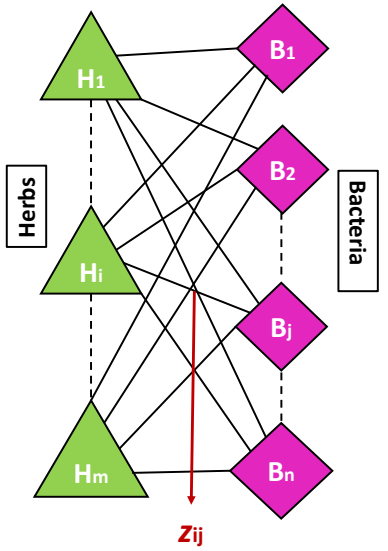


The MPBA

Graph Approximation

$$z_{ij} \approx \sum_{q=1}^{k} \frac{x_{iq}\, y_{jq}}{\sigma_q}$$, where





$$\sigma_q = \sum_{i=1}^{m} x_{iq} + \sum_{j=1}^{n} y_{jq}$$

It denotes the degree of the pathway nodes.

Matrix Form

$Z \approx X \Sigma Y^T$, where $\sum$ is a diagonal matrix , with $(\Sigma)_{qq} = \frac{1}{\sigma_q}$

The Divergence Loss Function

- To evaluate how well the algorithm models the data, we use the divergence loss function

- The approximation $Z \approx X\Sigma Y^T$, can be done minimizing

$$l(Z, X\Sigma Y^T)$$

Divergence Loss

$$l(Z, X\Sigma Y^T) = \sum_{i=1}^{m}\sum_{j=1}^{n}(z_{ij} log \frac{z_{ij}}{(X\Sigma Y^T)_{ij}} - z_{ij} + (X\Sigma Y^T)_{ij})$$

, which equal zero when $Z = X\Sigma Y^T$

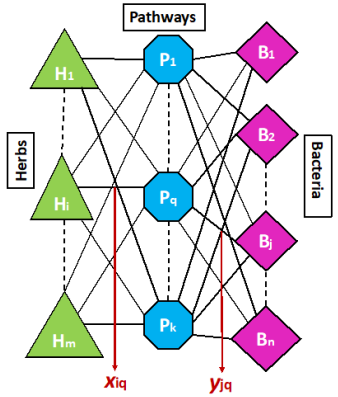
Probabilistic Graph Model

- We can interpret the same equation using ***Markov random walks*** on graphs as done using PLSA [T. Hoffman, 200].

- The weight z_{ij} is essentially a quantity proportional to the stationary probability of direct transitions between h_i and b_j, denoted by $p(h_i, b_j)$.

$$z_{ij} = p(h_i, b_j)$$

$$p(h_i, b_j) = p(h_i)p(b_j|h_i)$$

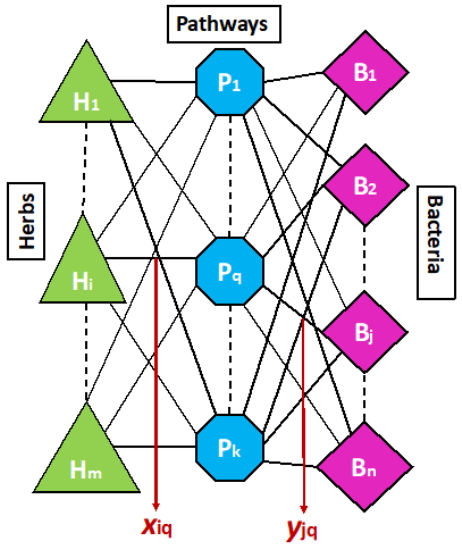


- In a tripartite graph there is no direct edge between the h_i node and the b_j node, and they can only be connected through the pathway nodes p_q

Probabilistic Graph Model

$$p(h_i, b_j) = p(h_i)p(b_j|h_i)$$ Transition probability

$$p(b_j|h_i) = \sum_{q=1}^{k} p(b_j|p_q)p(p_q|h_i)$$ Tripartite Network



$$p(h_i, b_j) = p(h_i) \sum_{q=1}^{k} p(b_j|p_q)p(p_q|h_i)$$ Back Substitution

$$p(h_i, b_j) = \sum_{q=1}^{k} \frac{p(h_i, p_q)p(b_j, p_q)}{p(p_q)} \Rightarrow z_{ij} \approx \sum_{q=1}^{k} \frac{x_{iq} b_{yq}}{\sigma_q}$$

Model Fitting Using EM Algorithm

Unsupervised Learning by Probabilistic Latent Semantic Analysis

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3.2. Model fitting with the EM algorithm

The standard procedure for maximum likelihood estimation in latent variable models is the Expectation Maximization (EM) algorithm (Dempster, Laird, & Rubin, 1977). EM

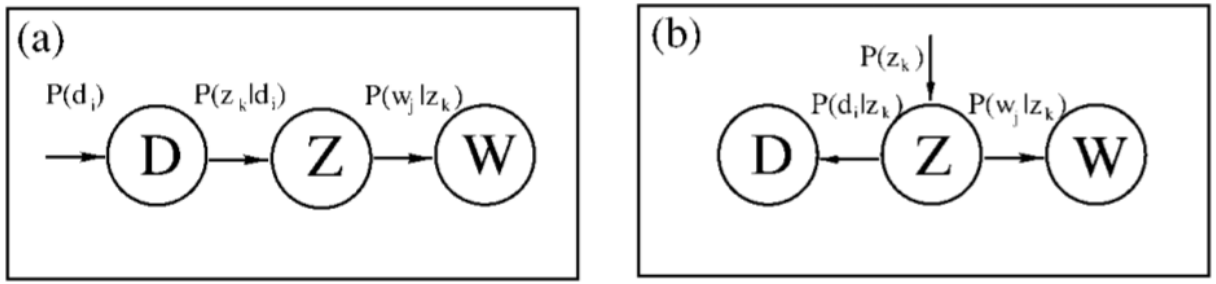


Figure 1. Graphical model representation of the aspect model in the asymmetric (a) and symmetric (b) parameterization.

Bayesian Formula

- For the E-step we apply Bayes' formula to obtain

$$p(p_q|h_i, b_j) = \frac{p(h_i, b_j|p_q)p(p_q)}{p(h_i, b_j)}$$

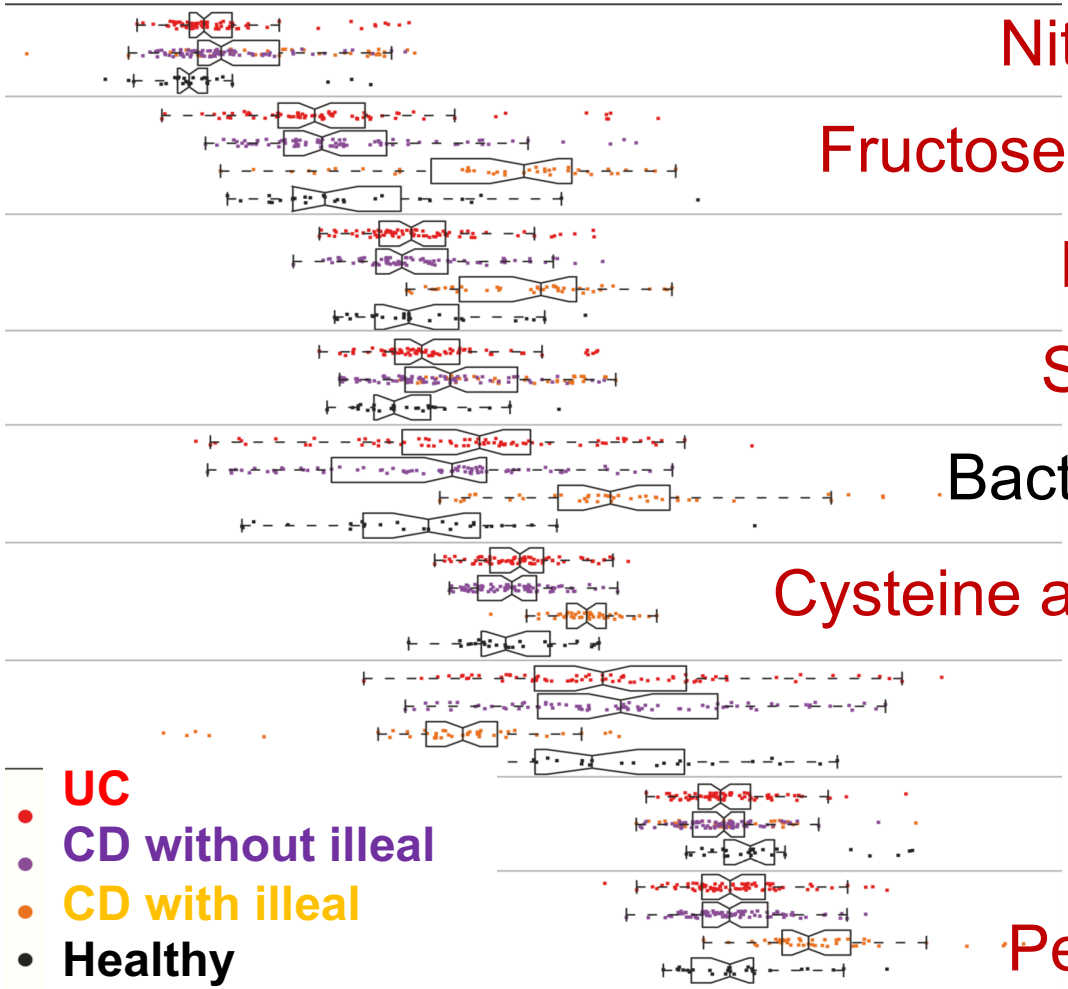
- And in the M-step one has to maximize the expected complete data log-likelihood given by,

$$\mathbf{E}\left[\mathcal{L}^c\right] = \sum_{i=1}^{N}\sum_{j=1}^{M} n(h_i,\ b_j) \sum_{q=1}^{K} P(p_q \mid h_i,\ b_j)\ \log\left[P(\ b_j \mid p_q) P(p_q \mid h_i)\right]$$

- where $n(h_i,\ b_j)$ is the frequency or the number of paths from herb to bacteria through the pathway node.

Dataset Used

Differential Abundant Pathways in IBD



Nitrogen metabolism

Fructose and mannose metabolism

Riboflavin metabolism

Sulfur metabolism

Bacterial secretion system

Cysteine and methionine metabolism

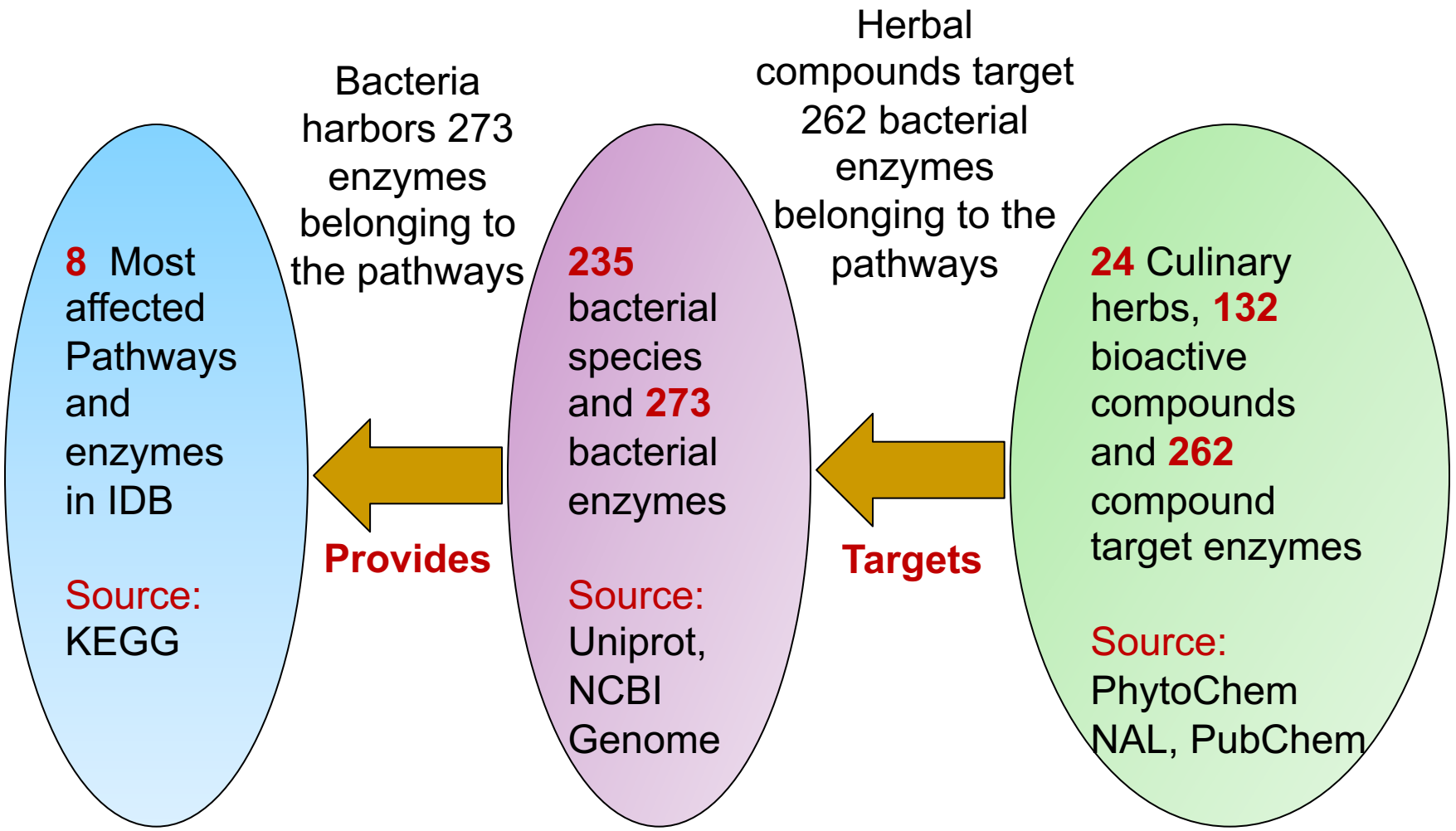
Butanoate metabolism

Lysine biosynthesis

Pentose phosphate pathway

2.X. C. Morgan, T. L. Tickle, H. Sokol, D. Gevers, K. L. Devaney,
3.D. V. Ward, J. A. Reyes, S. A. Shah, N. LeLeiko, S. B. Snapper, *et al.*, "Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment," *Genome biology*, vol. 13, no. 9, p. R79, 2012.

Dataset and Source



Results and Discussion

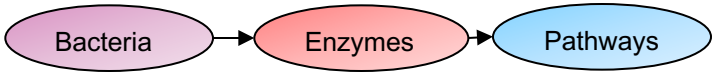
Case Study

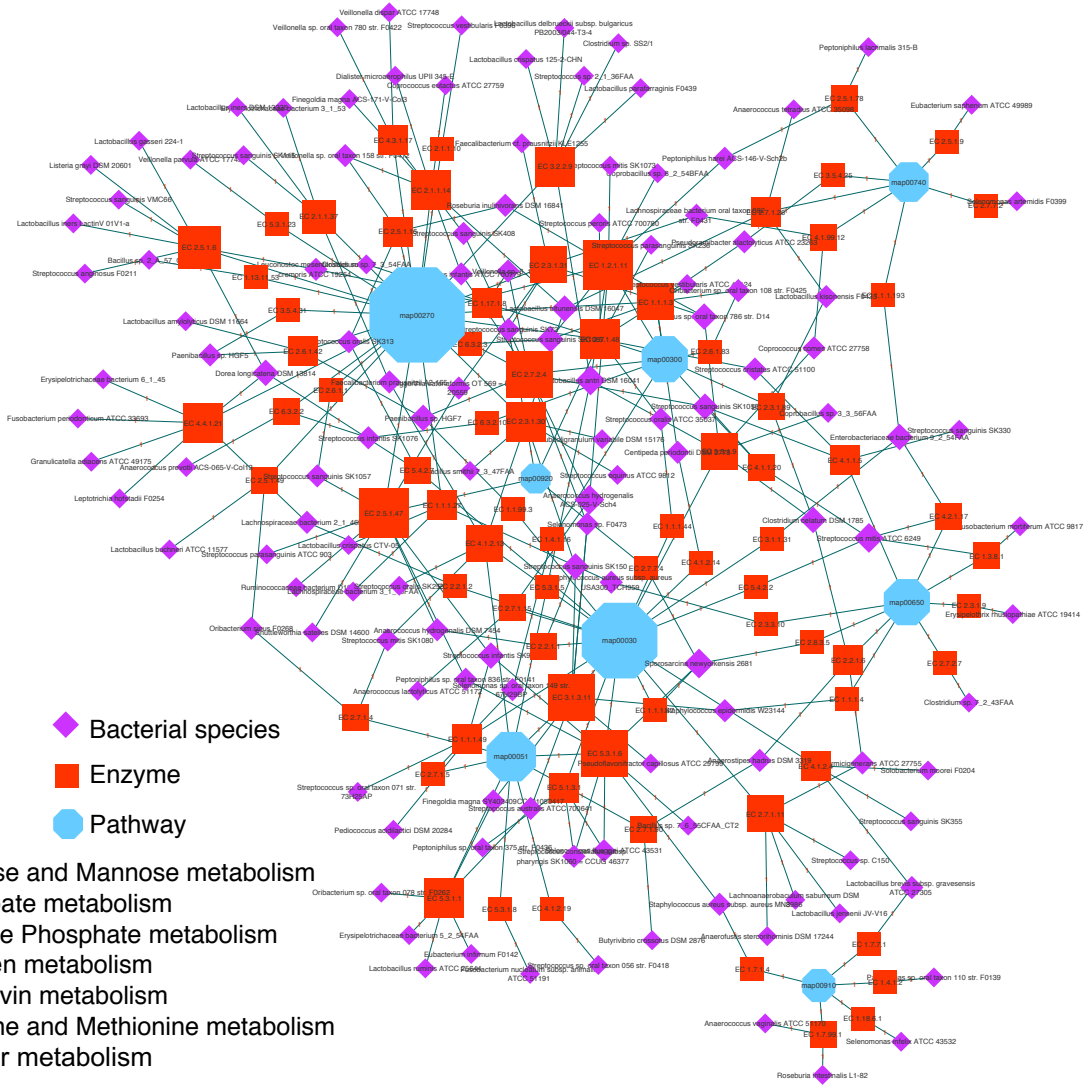
- Most Affected Microbial Metabolic Pathways and Enzymes In Both UC And CD

Pathway	Map	Enzyme Count	Bacteria Count
Cysteine and methionine metabolism	map00270	86	235
Butanoate metabolism	map00650	67	222
Fructose and mannose metabolism	map00051	60	235
Pentose phosphate pathway	map00030	53	235
Lysine biosynthesis	map00300	46	234
Niripartiterogen metabolism	map00910	37	217
Sulfur metabolism	map00920	44	195
Riboflavin metabolism	map00740	33	235

- Routes were traced through the metabolic model of the gut microbiota, and the organism(s) harboring the necessary genes identified.

Bacterial metabolism





- The network consists of **8** pathways, **273** bacterial enzymes, **235** bacterial species, and **18060** distinct interactions.

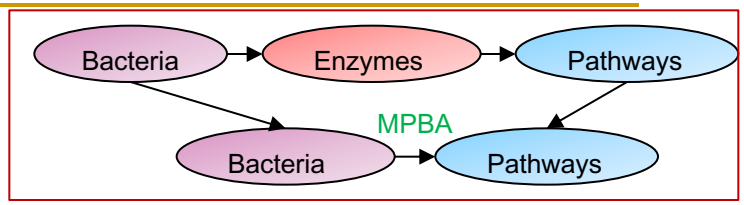
- *EC 1.2.1.11-aspartate-semialdehyde dehydrogenase*

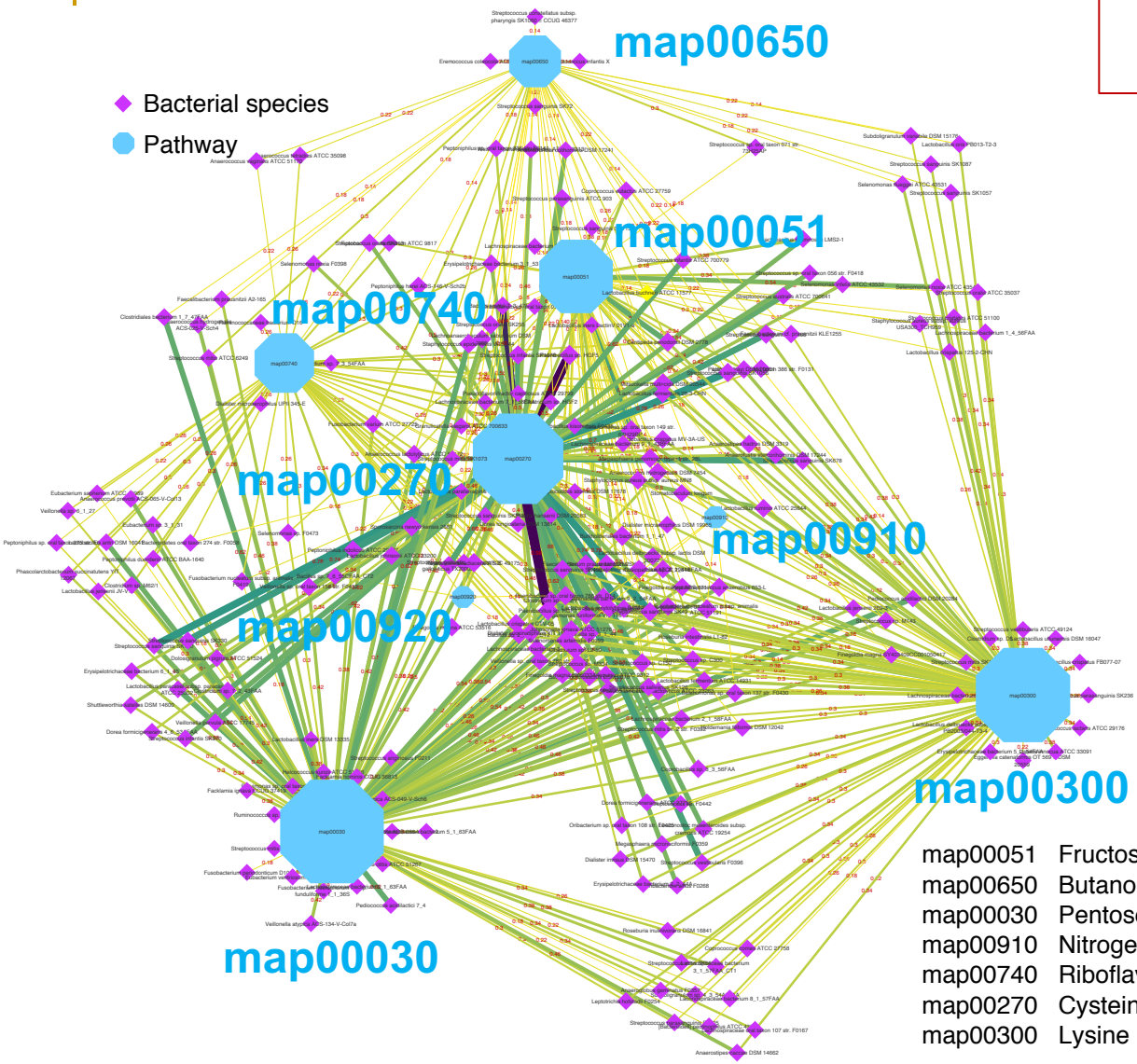
Uniquely Encoded Bacterial Enzymes

Potential Drug Targets

Enzyme	Pathway	Bacterium
$EC1.1.1.122 - L - fucosedehydrogenase$	Fructose and mannose metabolism	$CentipedaperiodontiiDSM2778$
$EC7.6.2.7 - taurineABCtransporter$	Sulfur metabolism	$Enterobacteriaceaebacterium9_254FAA$
$EC1.3.5.4 - fumaratereductase(quinol)$	Butanoate metabolism	$Enterobacteriaceaebacterium9_254FAA$
$EC2.3.1.184 - acyl - homoserine - lactonesynthase$	Cysteine and methionine metabolism	$Enterobacteriaceaebacterium9_254FAA$
$EC5.1.2.3 - 3 - hydroxybutyryl - CoAepimerase$	Butanoate metabolism	$Enterobacteriaceaebacterium9_254FAA$
$EC2.3.1.46 - homoserineO - succinyltransferase$	Sulfur metabolism,Cysteine and methionine metabolism	$Enterobacteriaceaebacterium9_254FAA$
$EC2.7.4.23 - ribose1,5 - bisphosphatephosphokinase$	Pentose phosphate pathway	$Enterobacteriaceaebacterium9_254FAA$
$EC2.7.1.51 - L - fuculokinase$	Fructose and mannose metabolism	$Enterobacteriaceaebacterium9_254FAA$
$EC3.1.3.7 - phosphoadenylate3' - nucleotidase$	Sulfur metabolism	$Enterobacteriaceaebacterium9_254FAA$
$EC2.7.1.55 - allosekinase$	Fructose and mannose metabolism	$EubacteriumventriosumATCC27560$
$EC1.13.12.16 - nitronatemonooxygenase$	Nitrogen metabolism	$Fusobacteriumnucleatumsubsp.animalisATCC51191$
$EC3.2.2.16 - methylthioadenosinenucleosidase$	Cysteine and methionine metabolism	$FusobacteriumvariumATCC27725$
$EC1.1.1.36 - acetoacetyl - CoAreductase$	Butanoate metabolism	$GranulicatellaadiacensATCC49175$
$EC4.1.1.12 - aspartate4 - decarboxylase$	Cysteine and methionine metabolism	$LactobacillusantriDSM16041$
$EC1.7.7.1 - ferredoxin - - - nitritereductase$	Nitrogen metabolism	$Lactobacillusbrevissubsp.gravesensisATCC27305$
$EC3.1.3.46 - fructose - 2,6 - bisphosphatase$	Fructose and mannose metabolism	$Lactobacillusdelbrueckiisubsp.lactisDSM20072$
$EC1.4.7.1 - glutamatesynthase$	Nitrogen metabolism	$LactobacillusrhamnosusLMS2 - 1$
$EC4.1.2.43 - 3 - hexulose - 6 - phosphatesynthase$	Pentose phosphate pathway	$Paenibacillussp.HGF7$
$EC1.1.1.215 - gluconate2 - dehydrogenase$	Pentose phosphate pathway	$Paenibacillussp.oraltaxon786str.D14$
$EC1.4.1.2 - glutamatedehydrogenase$	Nitrogen metabolism	$Parvimonassp.oraltaxon110str.F0139$
$EC2.3.3.14 - homocitratesynthase$	Lysine biosynthesis	$Peptostreptococcusanaerobius653 - L$
$EC2.7.7.22 - GDPmannosephosphorylase$	Fructose and mannose metabolism	$Selenomonassp.oraltaxon149str.67H29BP$
$EC2.8.3.5 - 3 - oxoacidCoA - transferase$	Butanoate metabolism	$Sporosarcinanewyorkensis2681$
$EC6.2.1.16 - acetoacetyl - CoAsynthetase$	Butanoate metabolism	$Sporosarcinanewyorkensis2681$
$EC6.2.1.2 - butyryl - CoAsynthetase$	Butanoate metabolism	$StaphylococcusepidermidisW23144$
$EC2.4.2.28 - MeSAdophosphorylase$	Cysteine and methionine metabolism	$Veillonellasp.oraltaxon158str.F0412$

Bacterial metabolism



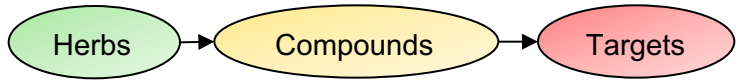


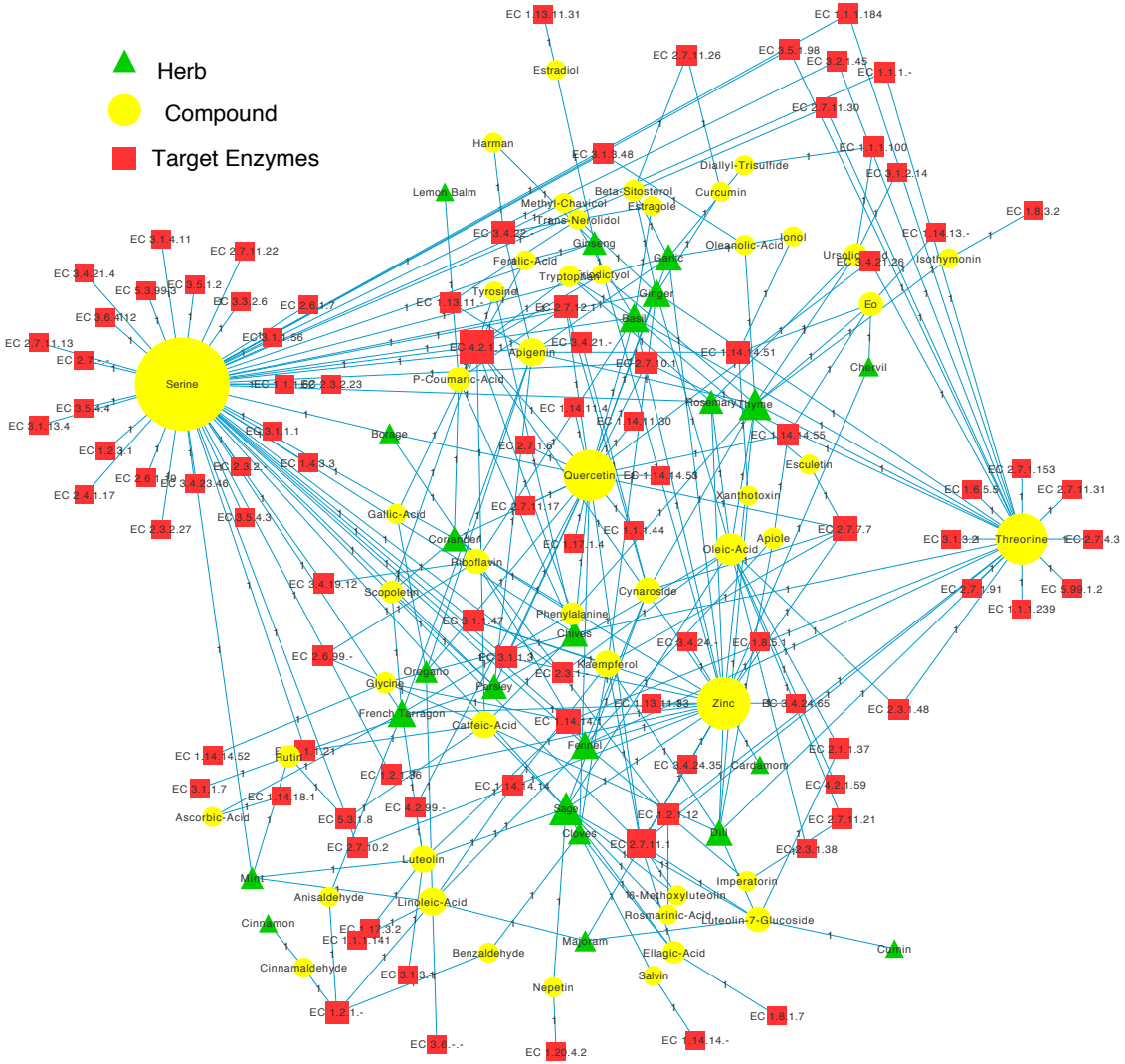
- *Paenibacillus sp. HGF7, Staphylo- coccus epidermidis W23144, Streptococcus sanguinis SK1087, Lactobacillus buchneri ATCC 11577*

- Sulphur and Nitrogen metabolism has enzymes uniquely encoded by bacterial species

map00051	Fructose and Mannose metabolism
map00650	Butanoate metabolism
map00030	Pentose Phosphate metabolism
map00910	Nitrogen metabolism
map00740	Riboflavin metabolism
map00270	Cysteine and Methionine metabolism
map00300	Lysine biosynthesis

Herbal Pharmacology



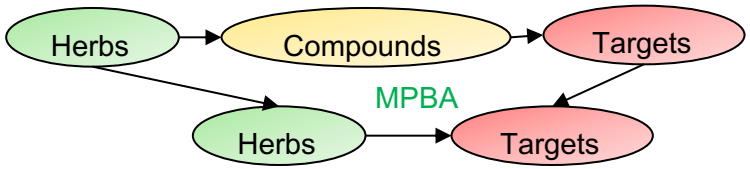


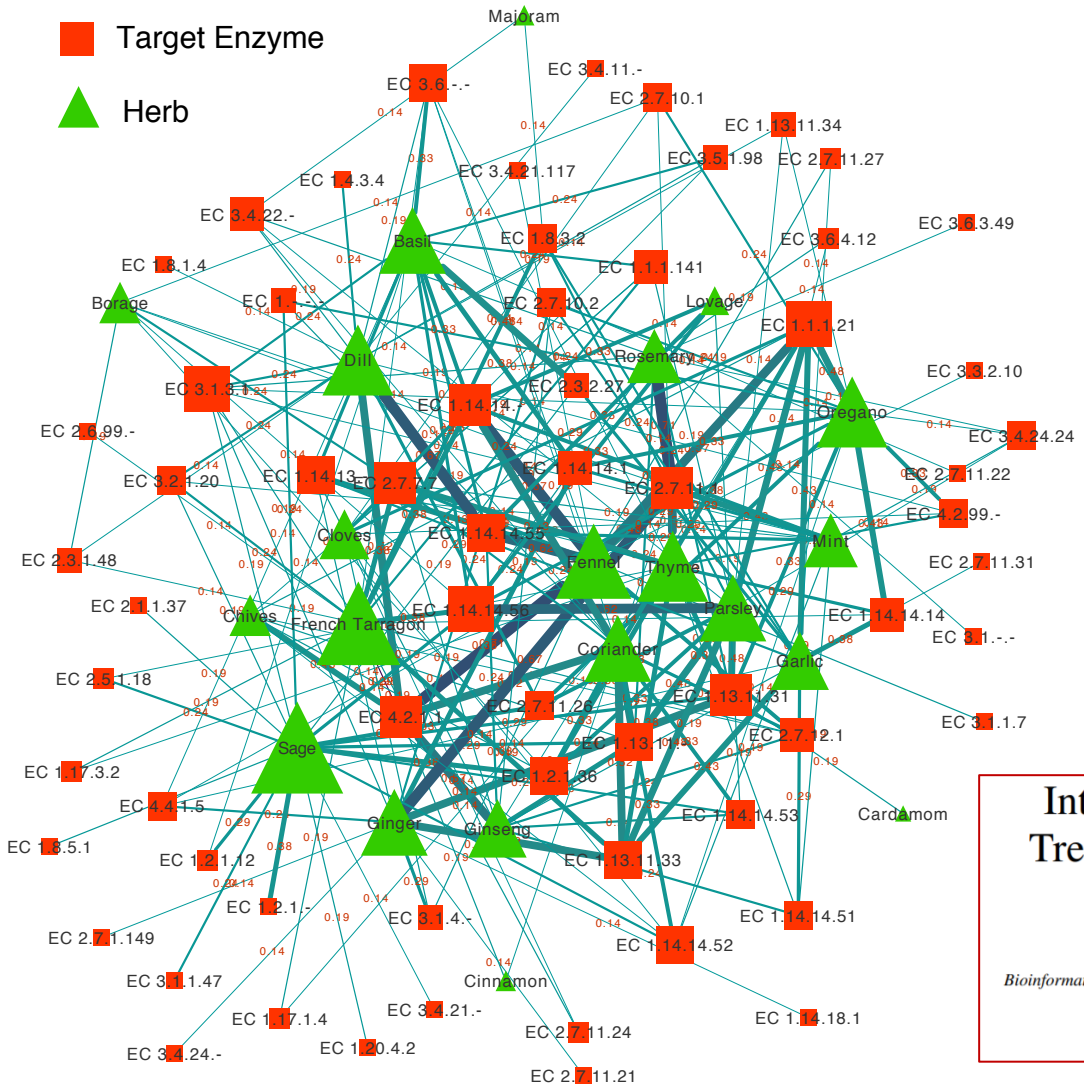
- The network **5623** unique herb-target interactions.
- Dill, fennel, parsley, ginseng, french tarragon, basil, coriander, mint, and thyme, were capable of targeting 262 enzymes.
- *aldehyde reductase* – most targeted enzyme, causes imbalances in 5-HT levels. [D. Keszthelyi, et al., 2009]

Compounds Targeting Enzymes

Compound	Enzyme_count	Herbs
Quercetin	185	Borage,Basil,Fennel,Dill,Chives,Coriander,Cloves, French Tarragon,Garlic,Oregano,Parsley,Ginger
Luteolin	180	Thyme,French Tarragon,Mint,Oregano,Rosemary,Sage
Curcumin	176	Ginger
Gallic-Acid	170	Thyme,Cloves,French Tarragon,Oregano,Sage
Nicotinamide	168	Ginseng
Coumarins	167	Dill,Lovage
O-Methoxycinnamaldehyde	167	Basil,Cinnamon
Guaiacol	167	Cinnamon,Mint
Lutein	167	Ginseng
Esculin	167	Basil
Linoleic-Acid	167	Borage,Basil,Cardamom,Fennel,Dill,Thyme,Chervil, Chives,Coriander,Garlic,Ginseng,Majoram, Mint,Oregano,Rosemary,Sage,Ginger
Estradiol	167	Ginseng
Apigenin	167	Basil,Dill,Thyme,Coriander,French Tarragon,Garlic, Oregano,Parsley,Rosemary,Sage
Myricetin	69	Cloves,Garlic,Ginger
Chlorogenic-Acid	49	Fennel,Dill,Thyme,Coriander,French Tarragon,Garlic, Majoram,Mint,Oregano,Parsley,Rosemary,Ginger
Esculetin	45	Basil,Dill,French Tarragon
Bergapten	16	Fennel,Dill,Coriander,Lovage,Parsley
5-Methoxy-Psoralen	16	Fennel,Dill,Coriander,Lovage,Parsley
Scopoletin	15	Fennel,Dill,Coriander,French Tarragon,Parsley
Benzaldehyde	14	Basil,Cinnamon,Cloves,Lemon Balm,Ginseng,Parsley

Herb-Target Analysis





- The HT network has **5623** unique herb-target interactions.
- The average degree (connectivity) of the HT network (**39.32**) and most herbs targeted on an average of **23.3** enzymes which is significantly higher than the modern synthetic drugs (**1.8**) [M.AY, et al., 2017].

Integrated Network-based Approach for the Treatment & Prevention of IBD with Natural Products

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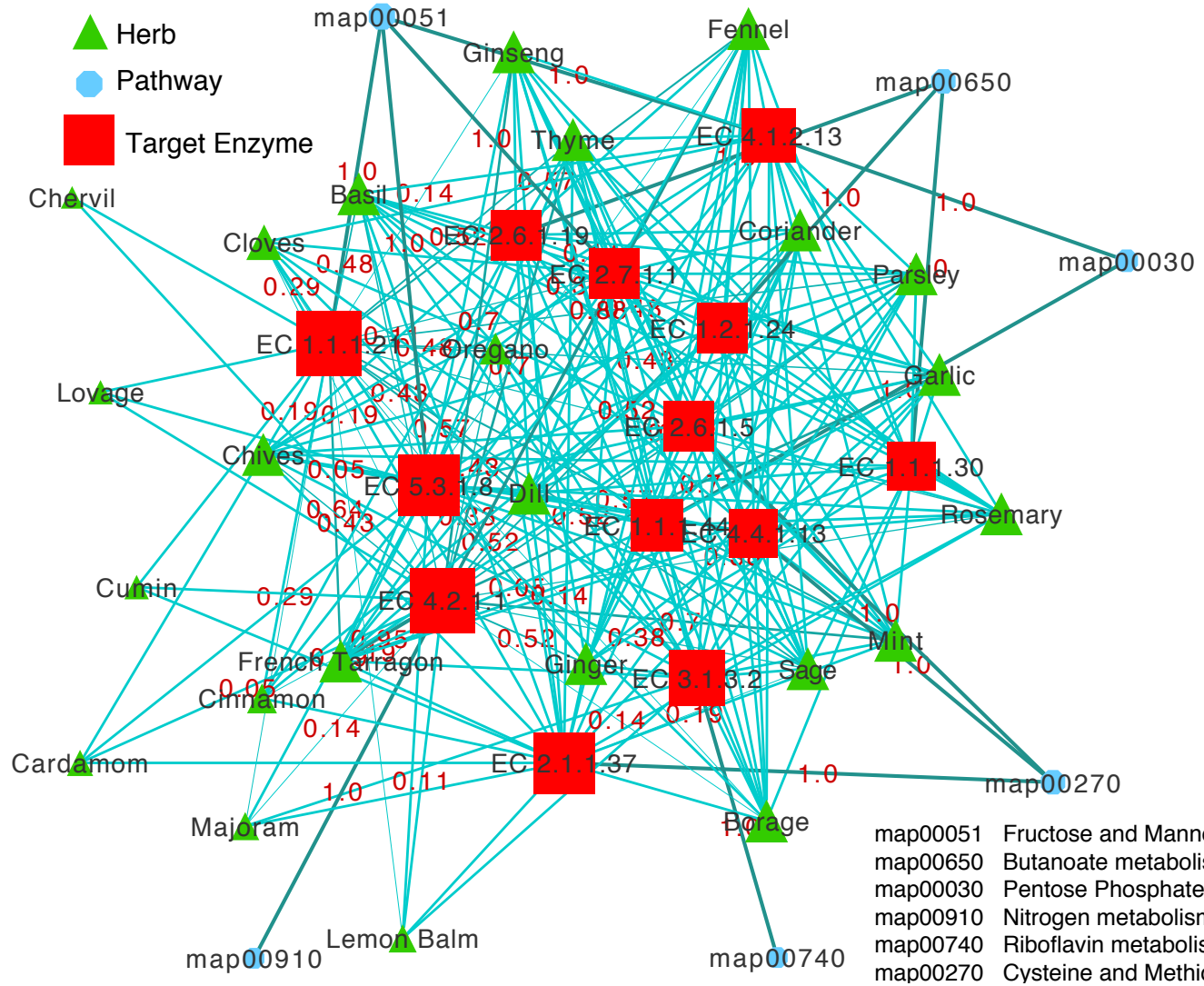
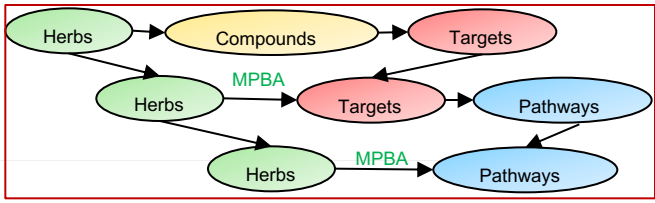
Herb-Target-Pathway Net

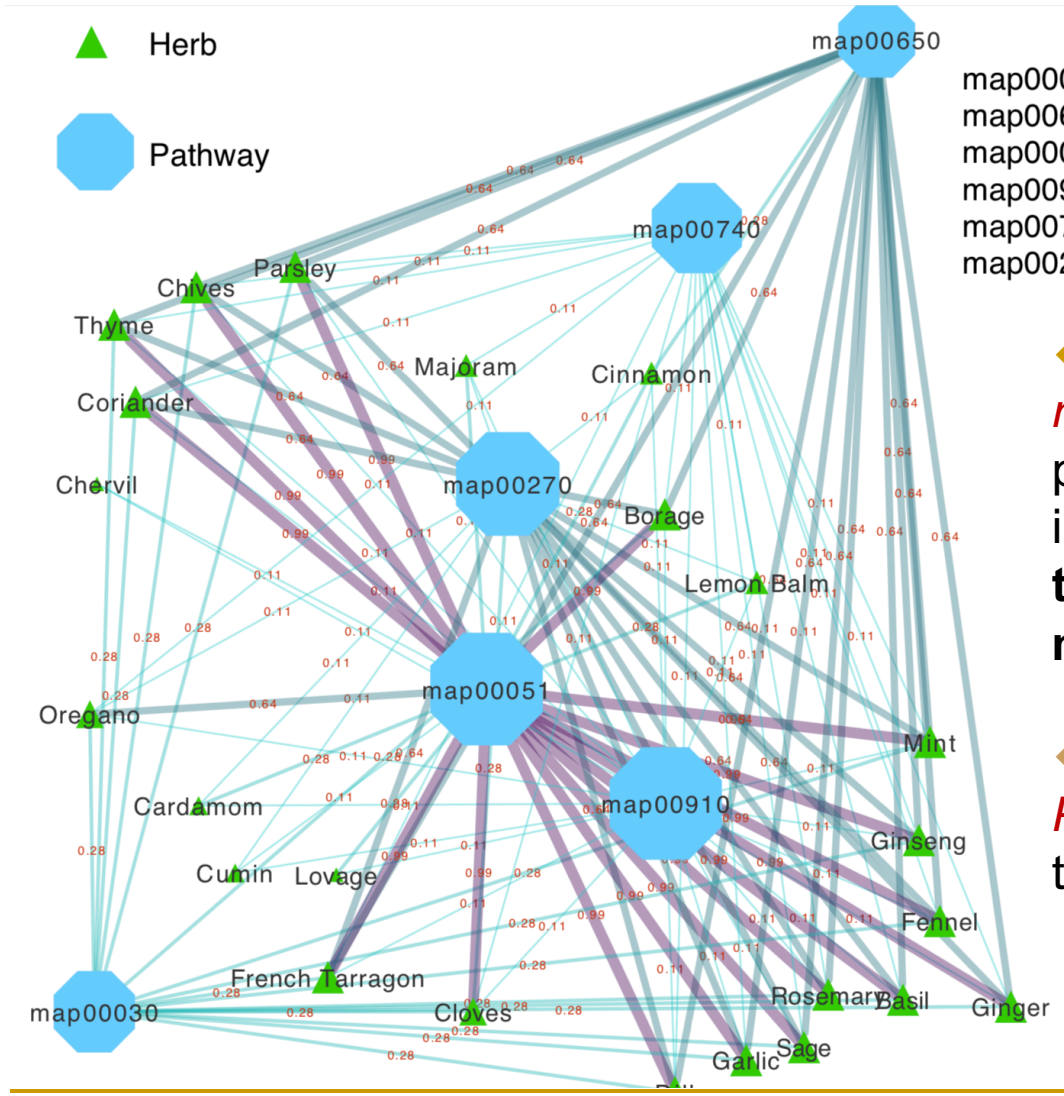


map00051 Fructose and Mannose metabolism
map00650 Butanoate metabolism
map00030 Pentose Phosphate metabolism
map00910 Nitrogen metabolism
map00740 Riboflavin metabolism
map00270 Cysteine and Methionine metabolism

- Herb-target-pathway (HTP) network was constructed with **24** herbs, **262** target enzymes, **8** metabolic pathways, and **5893** distinct interactions.

Herb-Pathway Analysis



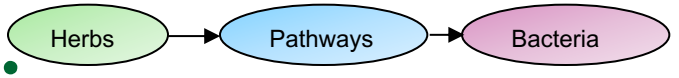


map00051 Fructose and Mannose metabolism
map00650 Butanoate metabolism
map00030 Pentose Phosphate metabolism
map00910 Nitrogen metabolism
map00740 Riboflavin metabolism
map00270 Cysteine and Methionine metabolism

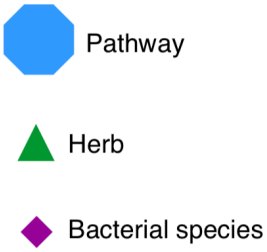
- *Fructose and Mannose metabolism (map00051)* is the pathway targeted by most herbs including, **coriander**, **chives**, **thyme**, **parsley**, **ginger**, **garlic**, **mint**, **basil**, etc.

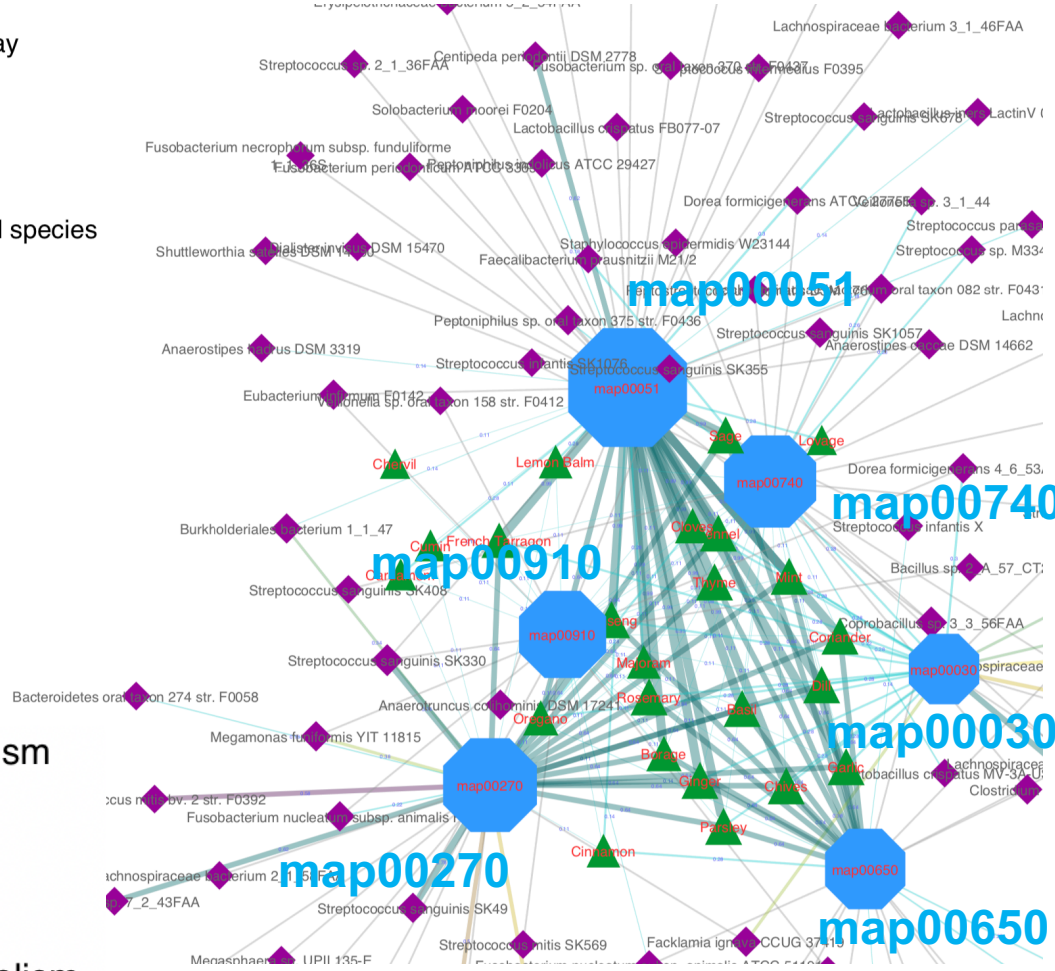
- *Butanoate* and *Pentose Phosphate* metabolism are targeted by fewer no. of herbs.

Herb-Pathway-Bacteria Net.



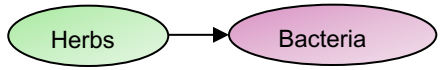
- *What are the potential herbs which can regulate bacterial functions and compositions?*
- What are the bacterial species a given herb can target?
- *And what are the metabolic functions the herbs can regulate?*

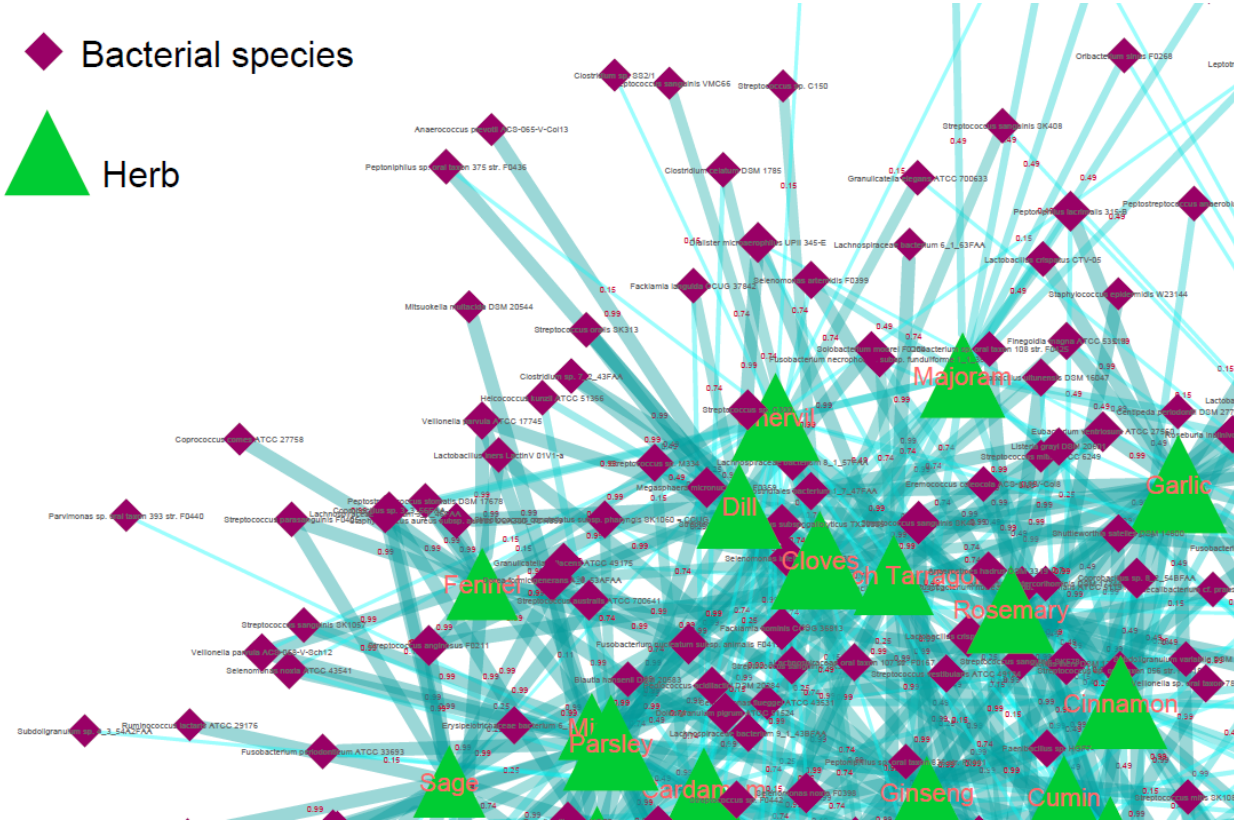




map00051	Fructose and Mannose metabolism
map00650	Butanoate metabolism
map00030	Pentose Phosphate metabolism
map00910	Nitrogen metabolism
map00740	Riboflavin metabolism
map00270	Cysteine and Methionine metabolism
map00920	Sulphur metabolism

Herb-Bacteria Analysis





- Species including *Sporosarcina newyorkensis 2681, Centipeda periodontii DSM 2778, Enterobacteriaceae bacterium 9 2 54FAA, Staphylococcus epidermidis W23144*, are targeted by various herbs - **mint, garlic, ginger, thyme, and, basil.**

- Alternatively, species including *Helcococcus kunzii ATCC 51366, Facklamia ignava CCUG 37419, Eubacterium infirmum F0142,* and *Fusobacterium necrophorum subsp. funduliforme 1 1 36S* are found to harbor unique enzymes which are not commonly encoded by the bacterial genes and are targeted by fewer herbs like **sage**, **borage**, etc

Discussion

- Herbal medicines, when exposed to gut microbes, metabolizes into active or absorbable compounds which are accomplished by the secreted enzymes of intestinal microflora.

- Results show ginseng has as an effect on 6 out of the 8 given pathways such as, Nitrogen metabolism, Fructose, and mannose metabolism, Riboflavin metabolism, Cysteine and methionine metabolism, Butanoate metabolism, and Pentose phosphate pathway, and can target 237 enzymes belonging to these pathways which can be harbored by 235 bacterial species.

- Ginseng exerted a weight loss effect (antiobesity) on gut microbiota in all participants, which differed depending on the composition of gut microbiota. [Mi-YoungSong, et at., 2014]

Conclusion

MPBA allows us to:

Identify what herbal compounds can affect the bacterial composition

- Understand the gut bacterial metabolism under normal or diseased condition.
- Functionally classify the gut microbiome through their metabolic pathways and the secreted enzymes.
- Understand the pharmacology and mechanism of action of the herbs.
- Model the effect of natural drug mechanism on the gut microbiome and in turn the host health.
- Integrate heterogeneous data and predict critical associations.
- Mathematically model complex biological systems like the herbs and gut ecosystem and provides a systems approach for characterizing the functions of the system.

Limitations

- The potential limitation that we encounter lies in the **incompleteness of the networks due to unavailable compound-target knowledge**.
- Difficulty in **differentiating the therapeutic effects from the side effects**, in spite of the large volume of data that currently exist.
- The proposed method could not identify **the type of activity of the bioactive compounds on the target enzymes**, except for some supporting literatures.

Future Work

- Include abundance information from clinical samples.

- Include other factors like, age, gender, environment, lifestyle, etc., which also play a vital role in shaping the microbiome of an individual.

Thank you

Questions

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