

VIRTUAL METABOLIC HUMAN



Connecting the microbiome and metabolome through metabolic modeling

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Diet-host-microbiota interactions

We know that nutrition influences

Health

Gut microbiota

Metabolome

Person-dependent

■ ■ ■



http://www.t-nation.com/free_online_article/sports_body_training_performance_nutrition/applied_nutrigenomics

We know less on **HOW** nutrition influences

Health

Gut microbiota

Disease-relevant metabolites

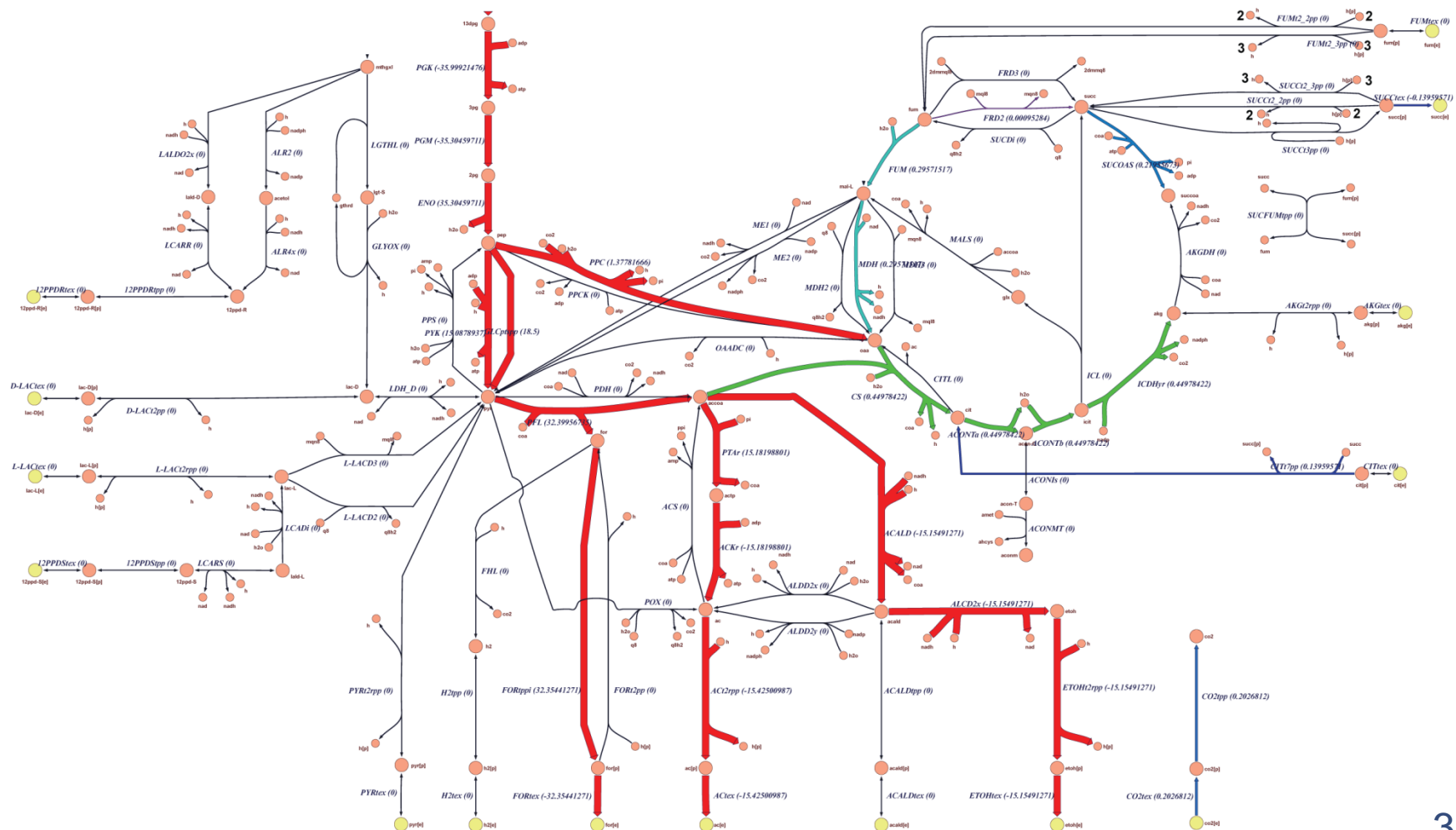
Mechanisms

■ ■ ■

We use computational models to link host-microbiome interactions to diet and the metabolome.

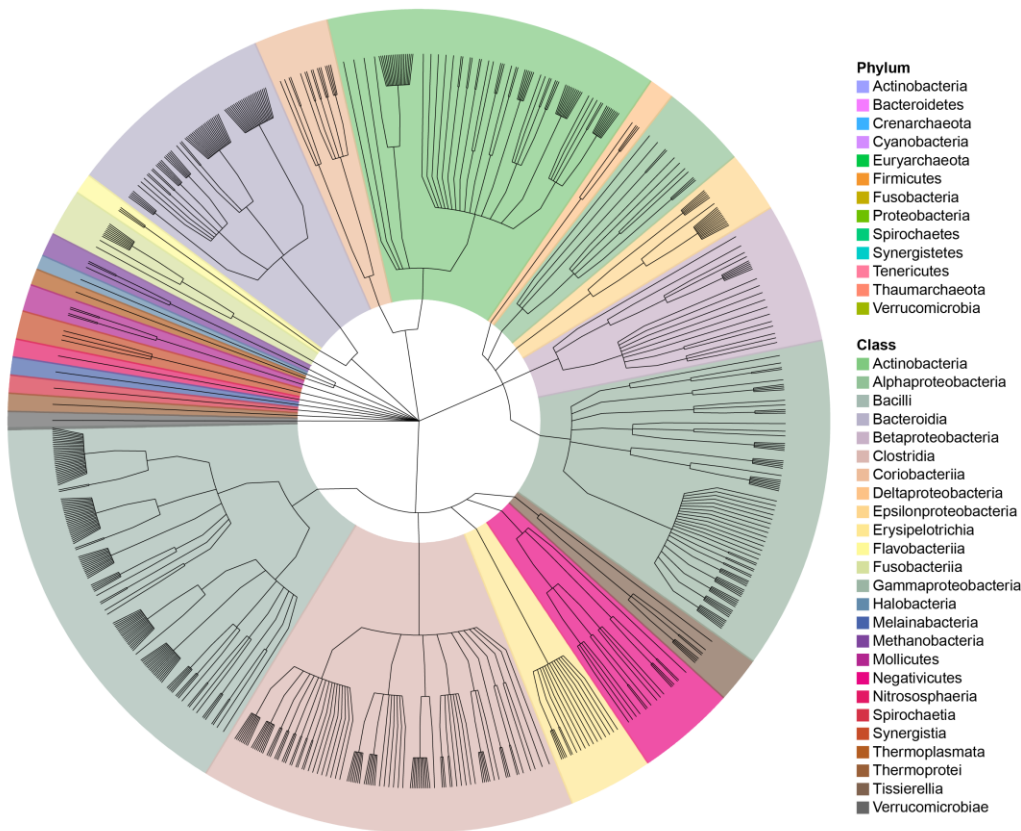
Constraint-Based Reconstruction and Analysis (COBRA):

- Bottom-up systems biology approach
- Relies on underlying genomic, biochemical, and physiological knowledge



Generation of genome-scale metabolic reconstructions for 773 members of the human gut microbiota

Stefanía Magnúsdóttir^{1,2}, Almut Heinken^{1,2}, Laura Kutt¹, Dmitry A Ravcheev¹, Eugen Bauer¹, Alberto Noronha¹, Kacy Greenhalgh¹, Christian Jäger¹, Joanna Baginska¹, Paul Wilmes¹, Ronan M T Fleming¹ & Ines Thiele¹



AGORA:
13 phyla
(now) 818 intestinal microbes
3,814 unique reactions
2,032 unique metabolites

AGORA is freely
available at
<https://vmh.life>

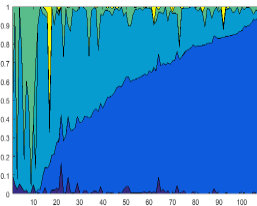


Personalized microbiome modeling with AGORA using a dedicated toolbox*

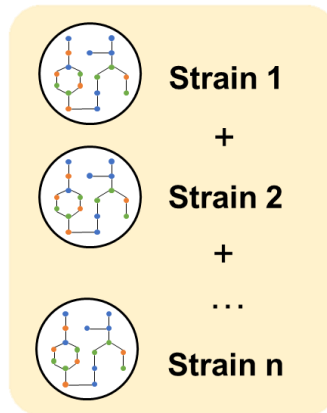
Metagenomic data** from
63 pediatric IBD patients without dysbiosis and 20 patients with dysbiosis
25 healthy control children
149 healthy adults



Reference set
of AGORA
genomes



Relative
abundances



Strain 1

+

Strain 2

+

...

Strain n



Simulated diet



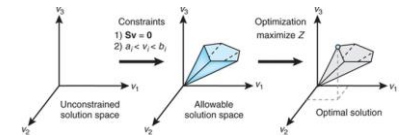
Diet Designer
(www.vmh.life)



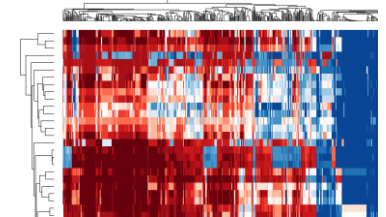
Personalized
community models



Constraint-based
modeling



Predicted
metabolic profiles

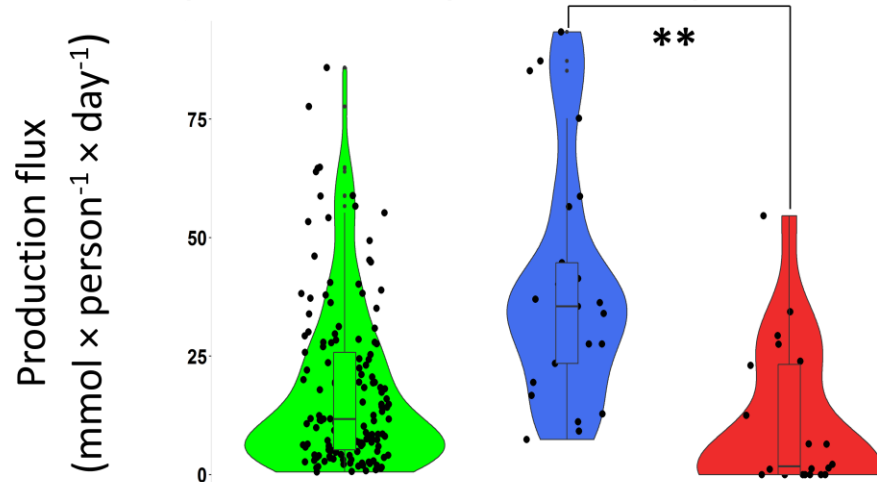


*Baldini, Heinken, et al., *Bioinformatics* 2018

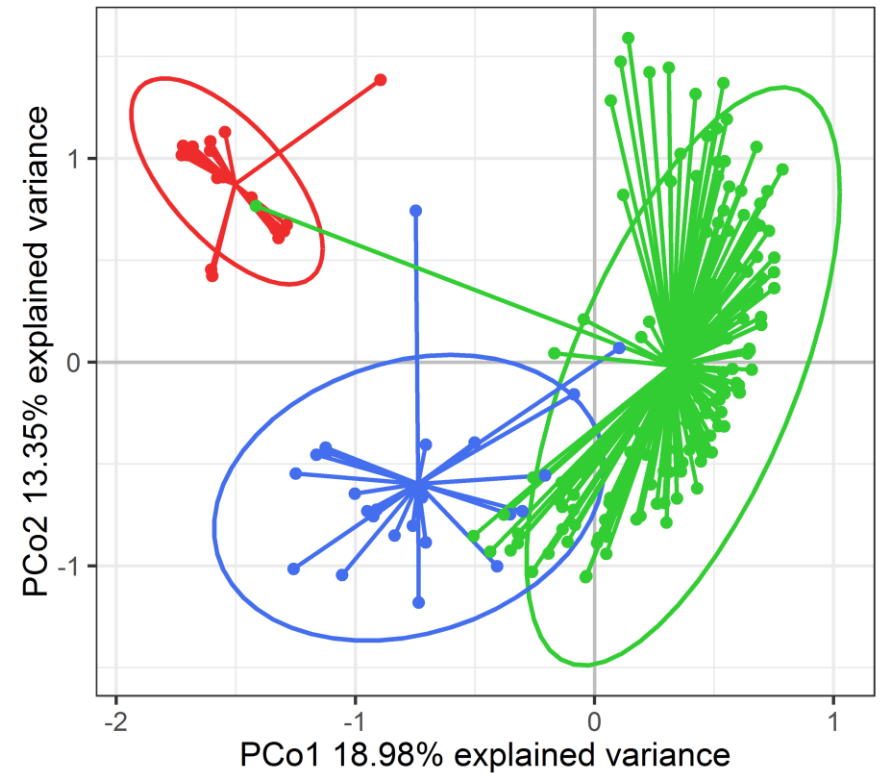
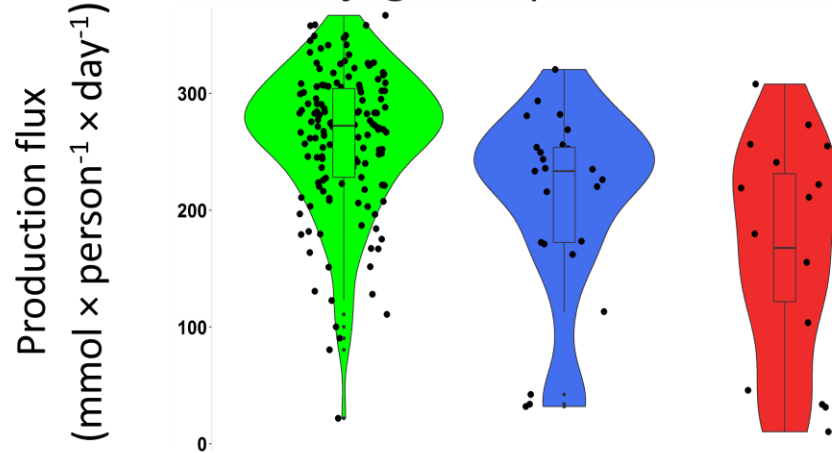
**Human Microbiome Project Consortium, *Nature* 2012, Lewis et al., *Cell Host & Microbe* 2015

Pediatric IBD patients with dysbiosis can be distinguished from healthy control children based on the computed bile acid production fluxes

12-dehydrocholate production potential



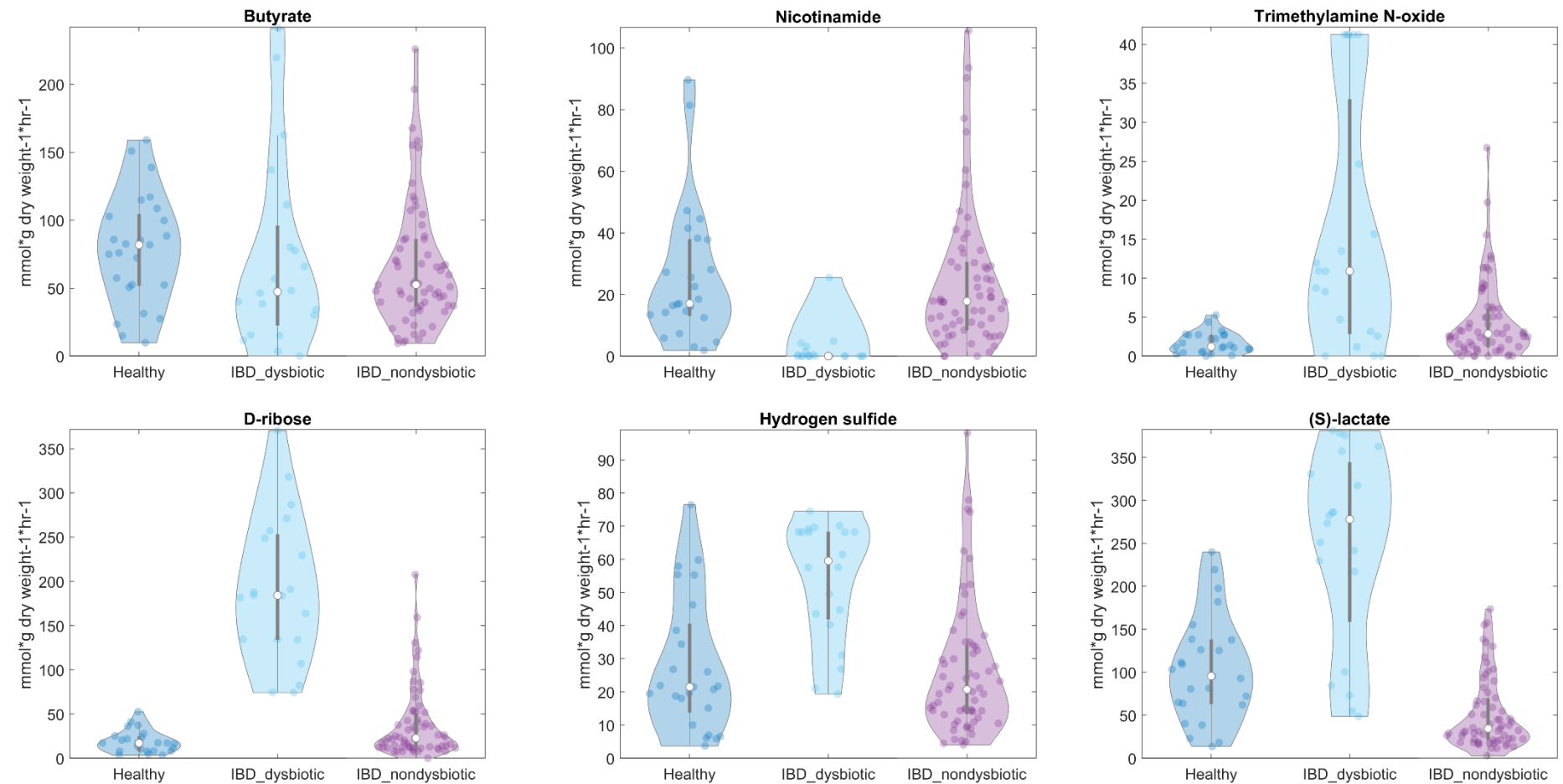
Cholate deconjugation potential



● Healthy_HMP
● IBD_pediatric
● Healthy_pediatric

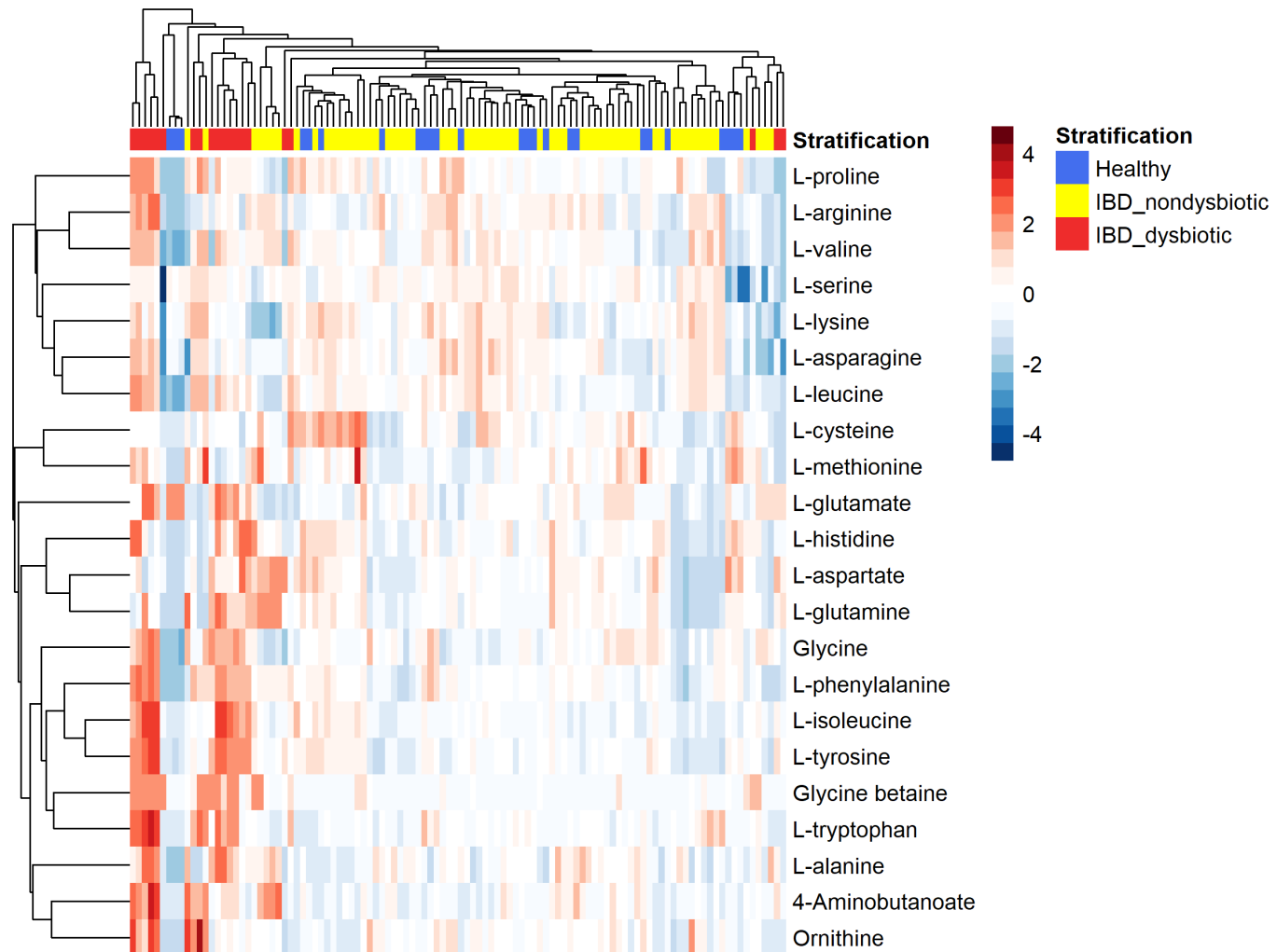
Predicted metabolic profile in healthy and IBD

- 25 healthy microbiomes, 63 non-dysbiotic Crohn's Disease microbiomes, 20 dysbiotic Crohn's Disease microbiomes
- 223 metabolites were produced → 93 metabolites statistically significantly different



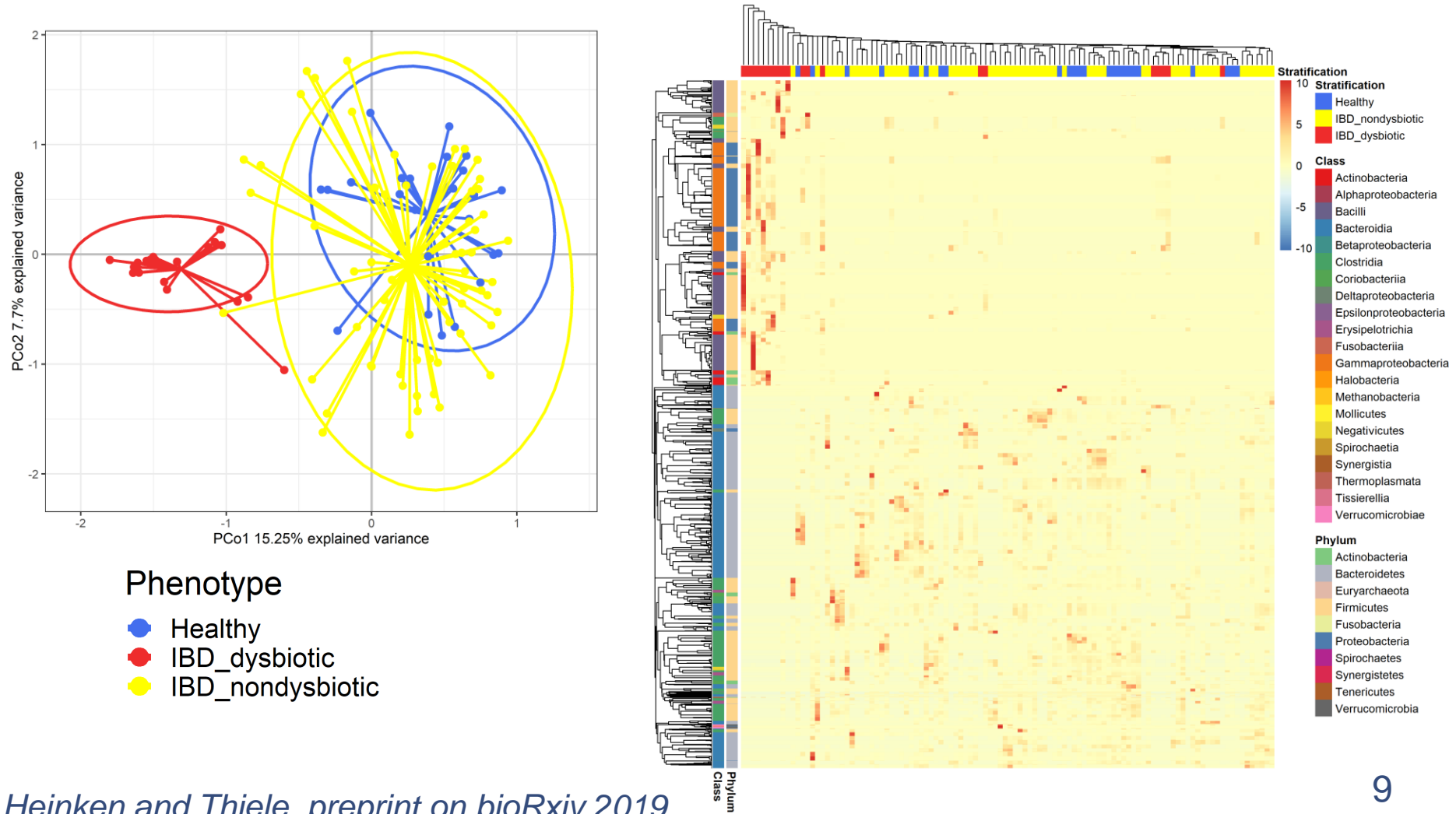
Dysbiotic IBD microbiomes are predicted to be enriched in amino acid production potential

Fecal amino acid concentrations were higher in dysbiotic IBD patients (Ni et al., Science Transl Med 2017).



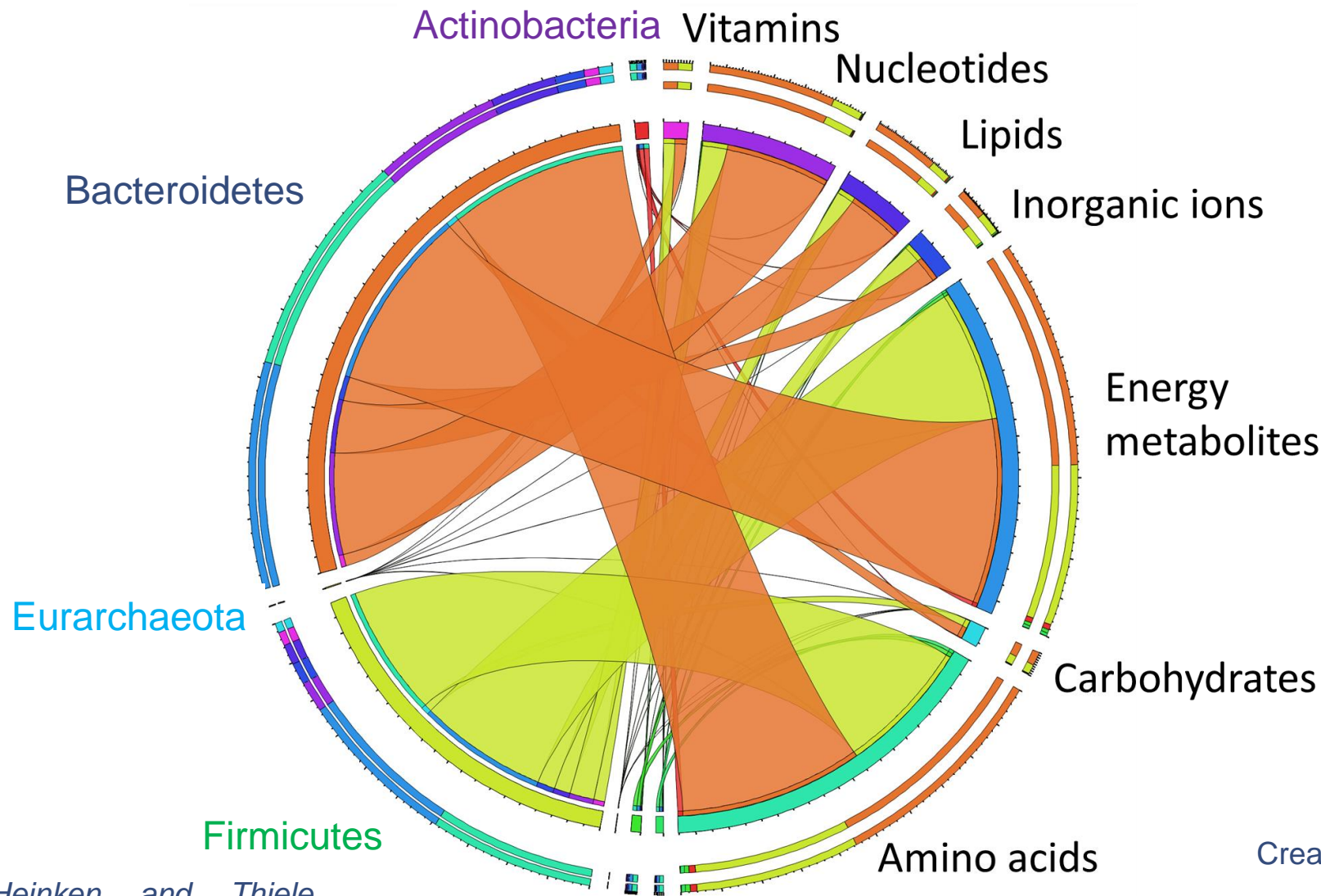
Strain-metabolite contributions clearly stratify dysbiotic IBD from nondysbiotic IBD and healthy microbiomes

Microbe-metabolite contributions were predicted in a strain-resolved, mechanistic manner.



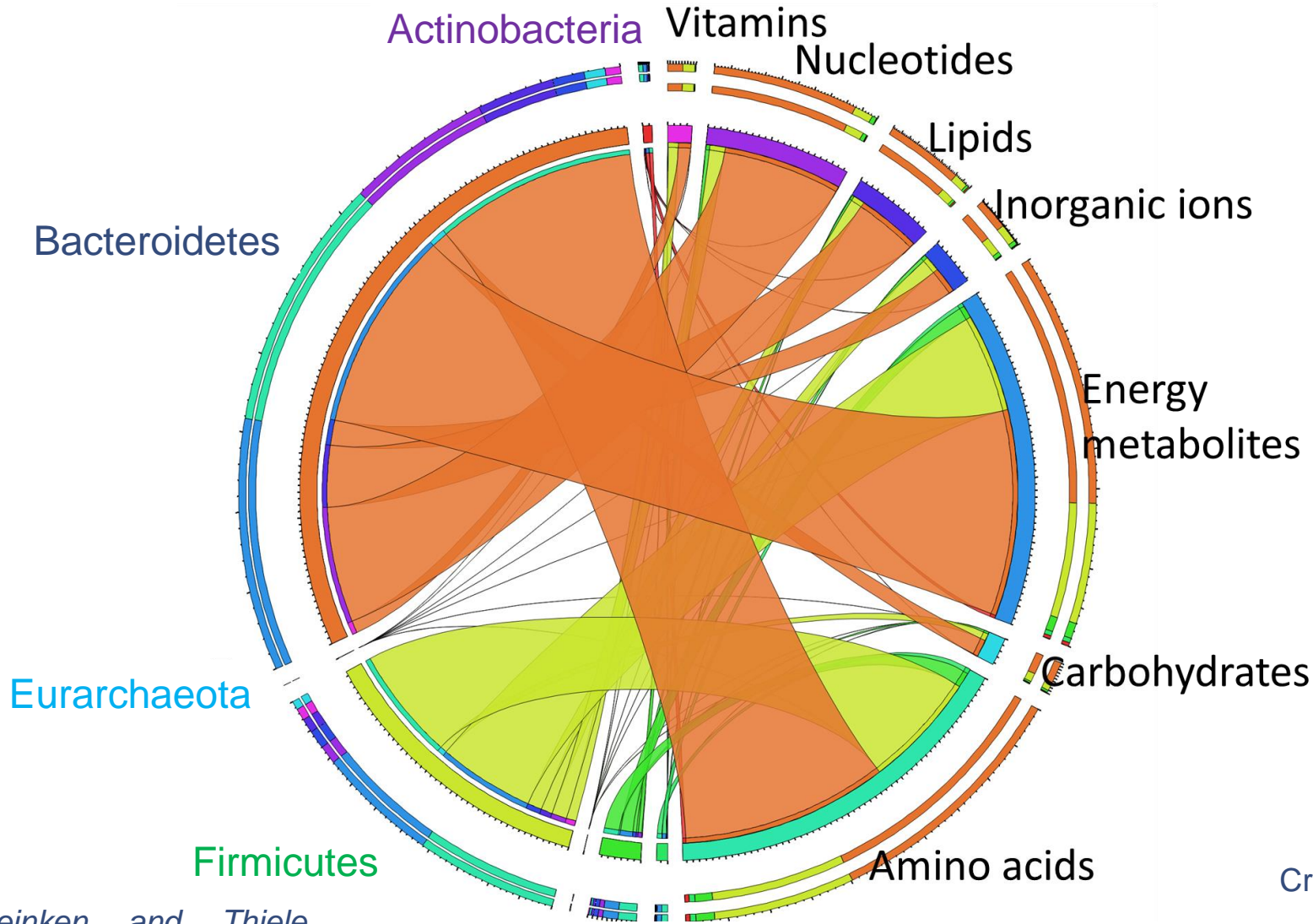
Microbe-metabolite contributions summarized by phylum and by subsystem

Healthy microbiomes



Microbe-metabolite contributions summarized by phylum and by subsystem

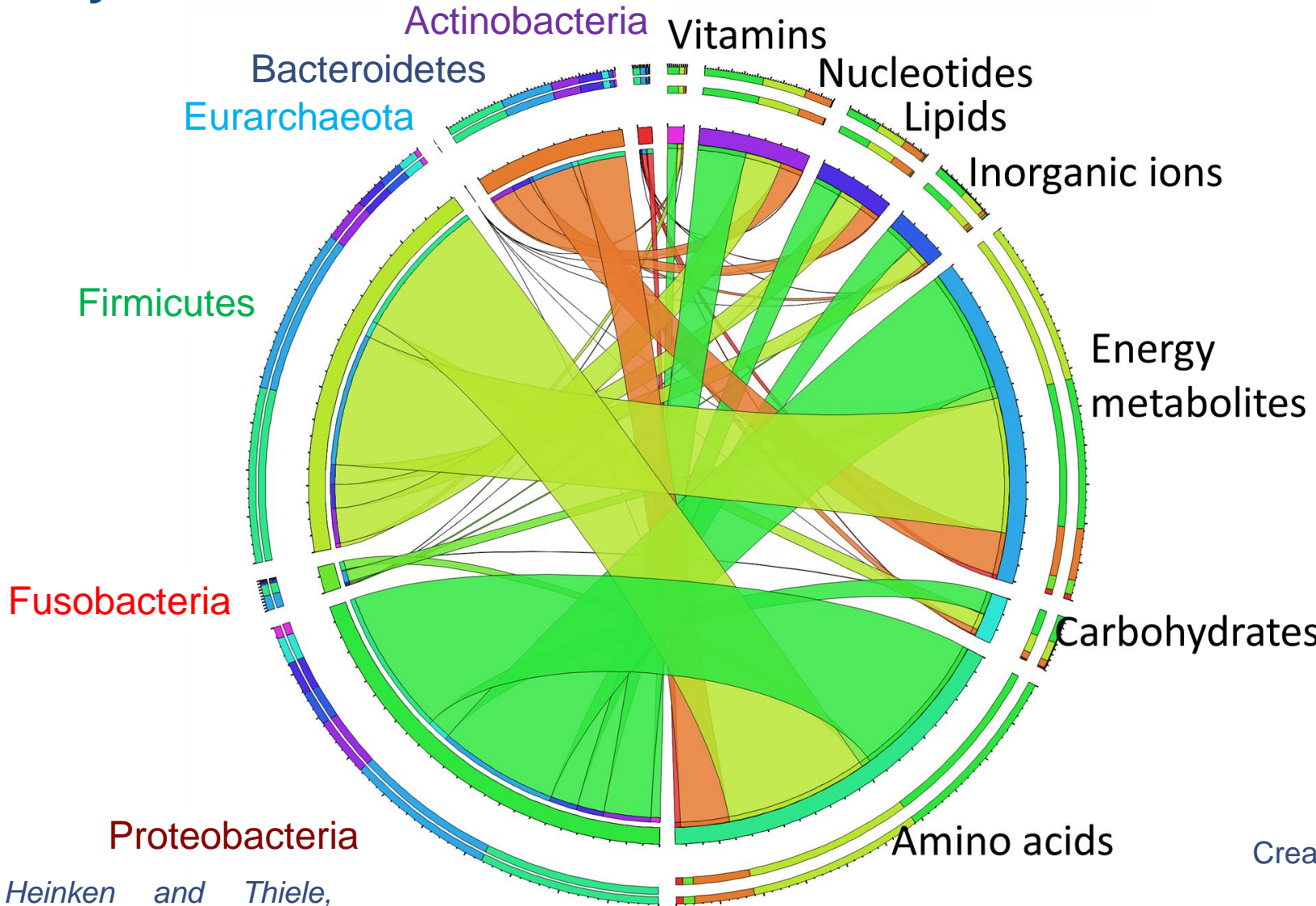
Non-dysbiotic IBD microbiomes



Created with Circos

Microbe-metabolite contributions summarized by phylum and by subsystem

Dysbiotic IBD microbiomes



Created with Circos

Summary/Outlook

- We use genome-scale reconstructions to build and interrogate personalized microbiome metabolic models.
- Predicted metabolic profiles were distinct in the dysbiotic IBD microbiomes.
- Strain-metabolite-contributions were systematically interrogated through computational modeling.
- Future applications will include personalized prediction of dietary and therapeutic interventions.

Acknowledgements

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