Reaction-Centered Metabolic Network Analysis

4th Munich Metabolomics Meeting

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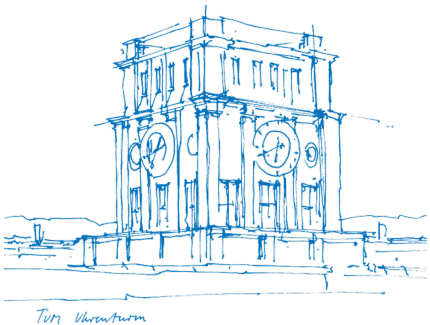
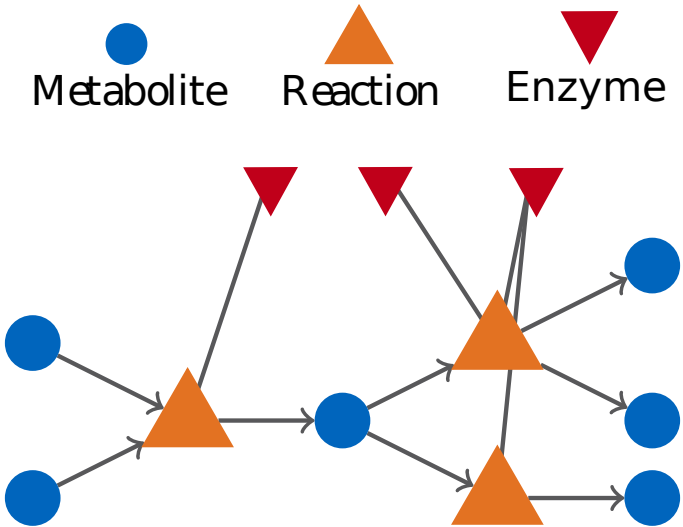


Motivation



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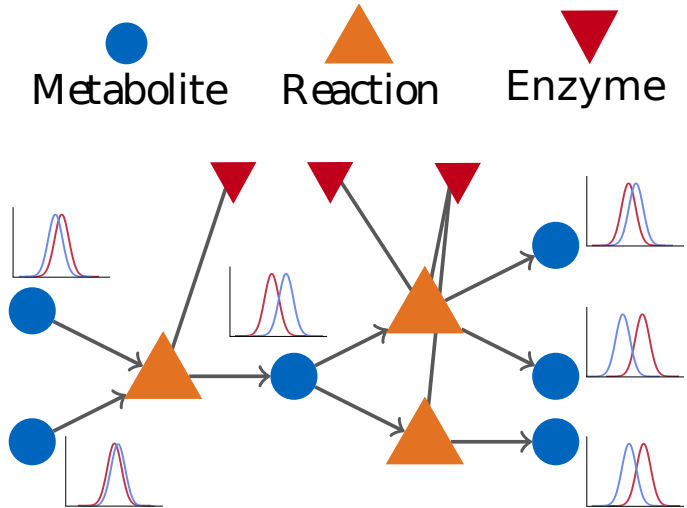

Motivation

$\Rightarrow$ **What can we learn about reaction activity?**

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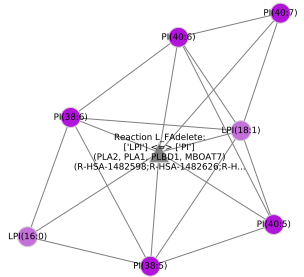

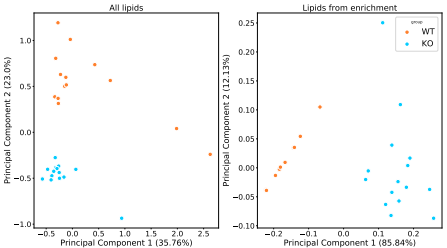

Lipid network and moiety analysis for revealing enzymatic dysregulation and mechanistic alterations from lipidomics data

Tim D. Rose, Nikolai Köhler, Lisa Falk, Lucie Klischat, Olga E. Lazareva, Josch K. Pauling

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This article is a preprint and has not been certified by peer review [**what does this mean?**].

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Objective from a Computational View

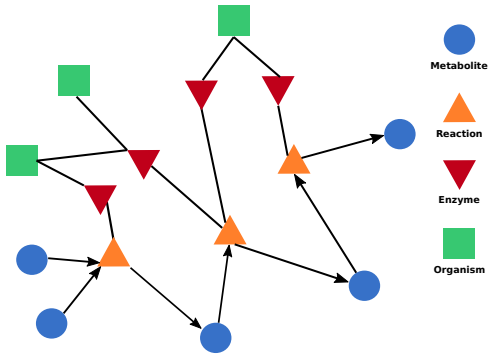
(Good) Approximation of reaction values can help to disentangle observations

$\Rightarrow$ Utilize information on reaction activity from *changes* in metabolic abundances

$\Rightarrow$ Use *complementary* information to separate disentangle metabolite- from reaction effects

Database Resource

Mammalian	Microbial
Reactome	KEGG
Recon 3D	AGORA
KEGG	



Metabolic Reaction Analysis

Goal: approximate activity change for each reaction in disease samples
Assumption: product abundances are dependent on substrate abundances

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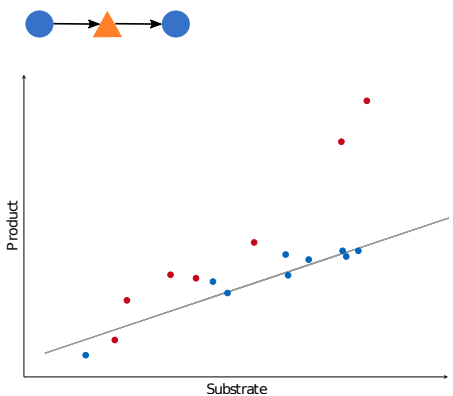
⇒ Linear model to estimate dependence



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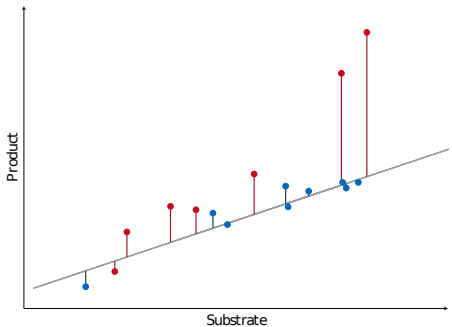
- Explained variance to estimate “goodness of fit”



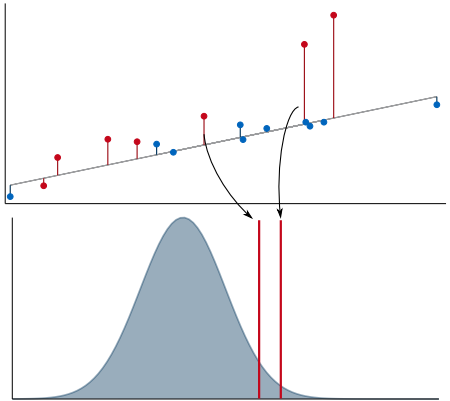
Metabolic Reaction Analysis

Goal: approximate activity change for each reaction in disease samples
Assumption: product abundances are dependent on substrate abundances

⇒ Linear model to estimate dependence

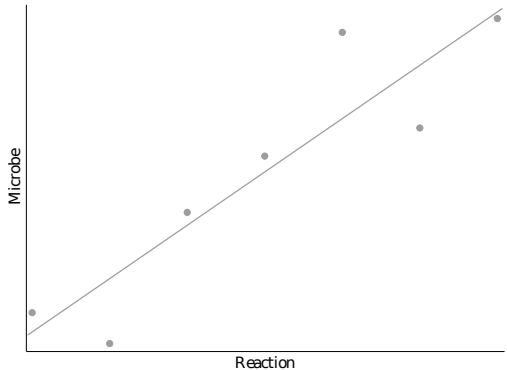
- Explained variance to estimate “goodness of fit”

⇒ one “reaction value” per reaction for *each* disease sample



Multi-omics Associations

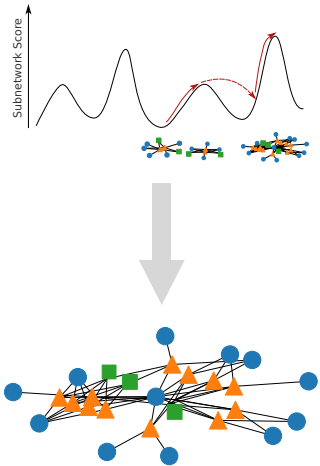
- Idea:
  association $\Rightarrow$ abundance changes when reaction does
- “Computational implementation”:
  correlation coefficient



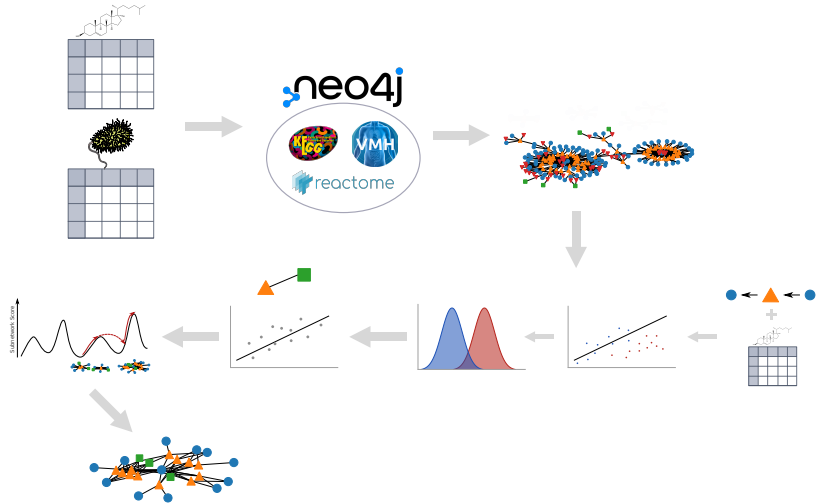
Subnetwork Identification

- Simple reporting
  - Reaction ranking
  - Association ranking
- Advanced reporting:
  find sets of *metabolically* connected reactions for which activity changes *and* microbial associations are high

⇒ Simulated-annealing supported local search
  - find connected reactions changing the most
  - Optionally: find parts of metabolism with the highest microbe-reaction association



Putting it all together...



Preliminary Results

LipiTUM

In-vivo Experiment by Zimmermann-Kogadeeva et al.[1]

- Mouse groups
  - Microbiome: germ-free, defined culture
  - Diet: control, high-fat
- $\sim$ 50,000 measure features
- $\sim$ 4,000 identified metabolites
- additional metagenomics data

[1] Zimmermann-Kogadeeva et al., "Multiomics and quantitative modelling disentangle diet, host, and microbiota contributions to the host metabolome" , bioRxiv 2022

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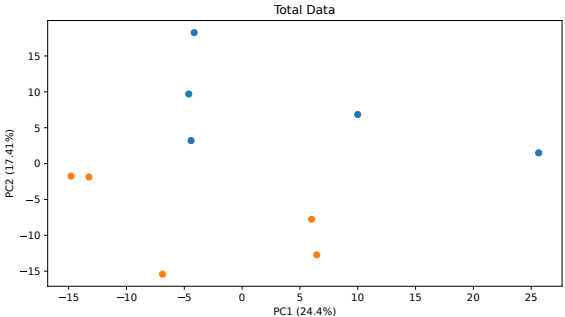

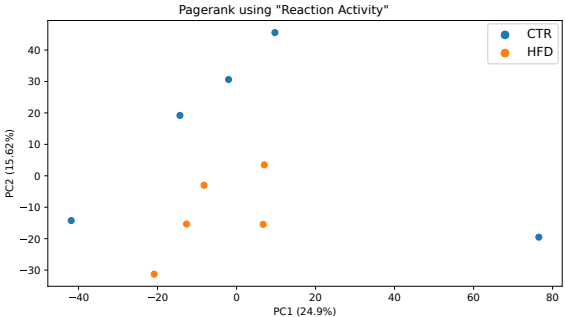

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Acknowledgments

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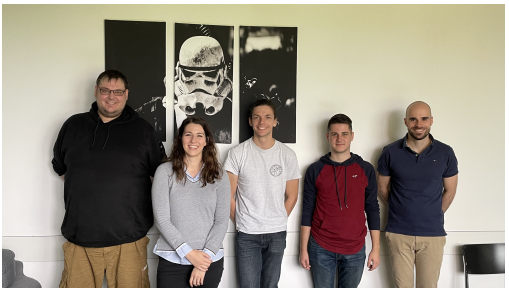

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Thank You!