Identification of characteristic features of metabolic states using Genome-Scale Metabolic Models

Chaitra Sarathy[1,**], Marian Breuer[1], Martina Kutmon[1,2], Michiel E. Adriaens[1], Chris T. Evelo[1,2], Ilja C. W. Arts[1,3]

Maastricht University, The Netherlands: [1] Maastricht Centre for Systems Biology (MaCSBio), [2] Department of Bioinformatics – BiGCaT, NUTRIM Research School, [3] Department of Epidemiology, CARIM School for Cardiovascular Diseases

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** Presenting author @chaitrasarathy
E-mail: chaitra.sarathy@maastrichtuniversity.nl

Maastricht University
macsbio
MAASTRICHT CENTRE FOR SYSTEMS BIOLOGY
provincie limburg
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MOTIVATION

Metabolism: Central role in maintaining cell functionality

Metabolic dysfunctions: Obesity, Type II diabetes, Neurodegenerative diseases & cancer

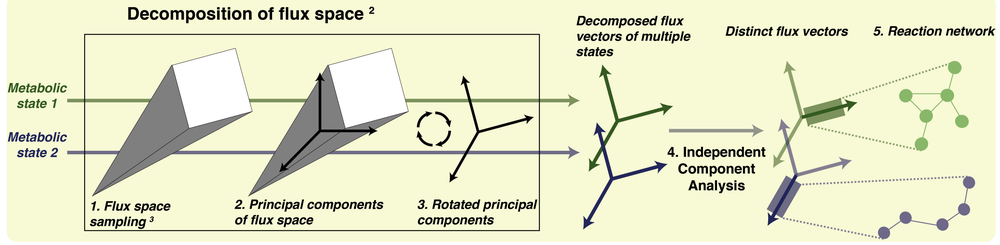
Need for systems-level understanding of cellular physiology

OBJECTIVE

• Develop a method to compare metabolic states using genome-scale metabolic models

• Biological application: Modify BCAA uptake in adipocyte
BCAA: branched chain amino acids – leucine, isoleucine & valine

METHODS



1. Identify flux distributions of all reactions

2. Identify flux vectors that explain variation in the flux space (Flux vectors: Linear combination of reaction fluxes)

3. Transform flux vectors into biochemical space

4. Identify flux vectors that are distinct between metabolic states

5. Construct network of reactions

Model: human adipocyte [1] Simulated conditions: Unconstrained (unlimited BCAA uptake) vs Constrained (no BCAA uptake)

Figure 1: Workflow for comparing metabolic states developed in this study

RESULTS

Reaction fluxes

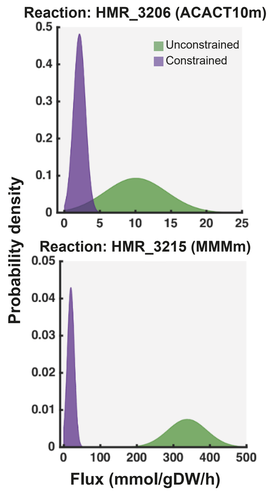


Figure 2: Two of the simulated reaction fluxes

Reduced BCAA metabolism on blocking BCAAs

Flux Space Sampling

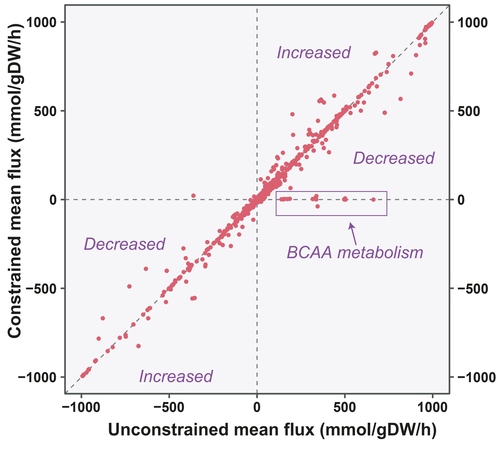


Figure 3: Comparison of mean fluxes between simulated conditions

Strong similarity in fluxes between the simulated metabolic states

PCA on flux spaces

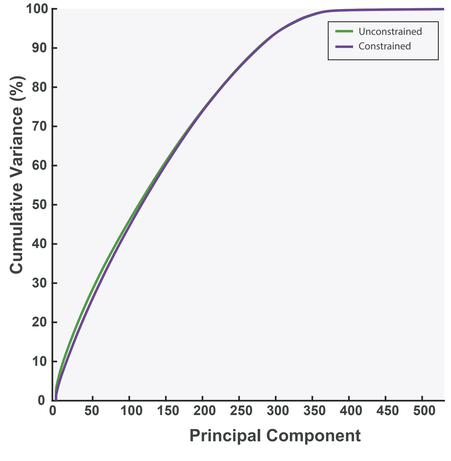


Figure 4: Cumulative variance explained by principal components

About 200 out of 4067 flux vectors explain 75% variation in both flux spaces

Distinct flux vectors

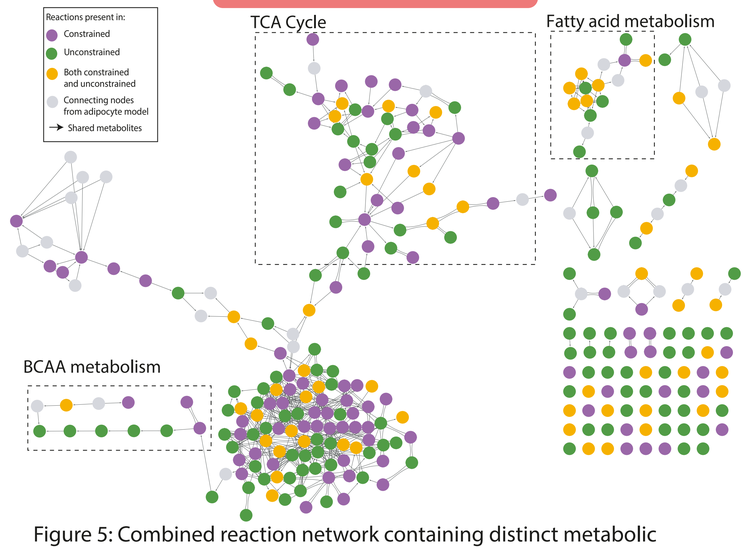


Figure 5: Combined reaction network containing distinct metabolic processes visualized in Cytoscape

BCAA breakdown links to TCA cycle & Fatty acid metabolism

Simulations indicate:

• Changes in metabolite uptake/release profile

• Close relationship between metabolism of BCAAs and other amino acids: glycine, arginine, proline & tyrosine

CONCLUSION

• Developed a scalable method for comparing metabolic states

• Extracted biochemically meaningful features from adipocyte model

REFERENCES

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2. Barrett et al., DOI: 10.1186/1752-0509-3-30
3. Braunstein et al., DOI:10.1038/ncomms14915