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Genome-scale metabolic models for personalized nutrition and healthy aging

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Genome-scale metabolic models (GSMM)

What are they?

Computational reconstructions and simulations of large-scale metabolic networks

Aim: To understand how diet impacts the aging process, and to find dietary interventions to slow the pace of aging, with a focus on skeletal muscle.

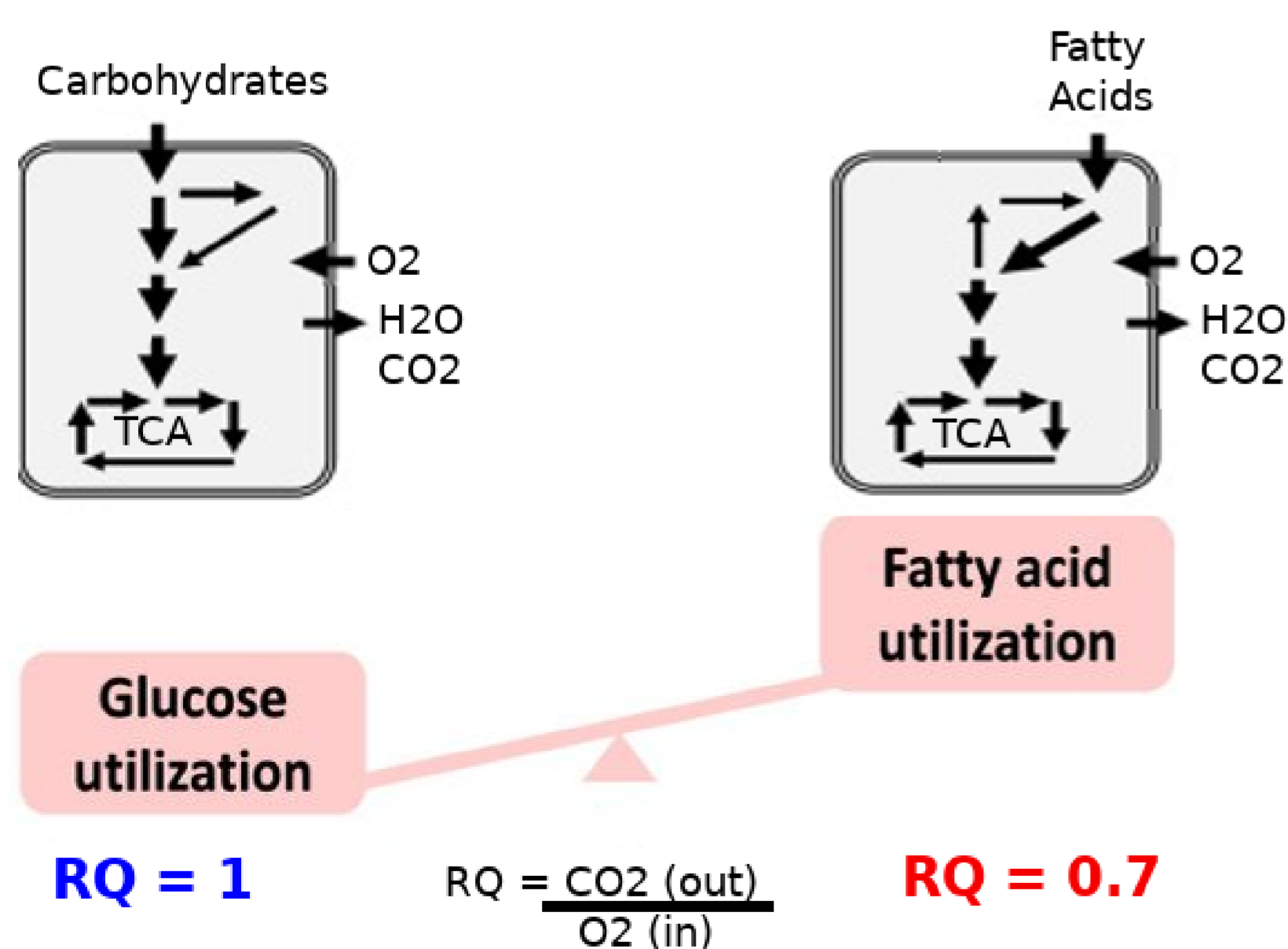
How: Patient-derived genome-scale models, are built from muscle gene expression data of young and older subjects, using the CORDA algorithm [1] and a human metabolic network reconstruction, Recon 2.2 [2].

Flux Balance Analysis (FBA) [3] is then used to simulate metabolic flexibility (RQ) and protein synthesis rate between individuals.

	Old (n=58)	Young (n=69)
Average Number of Reactions	3331.00	3347.47
Average Number of Metabolites	2430.22	2434.02
Average Number of Genes	1234.22	1236.74

Table 1: Summary of the 127 patient-derived metabolic models generated during this study

Metabolic flexibility



• Metabolic flexibility is the ability to **readily adapt to changes in fuel availability** (e.g. between glucose and fatty acids) [4] and is associated with **metabolic health and longer lifespan** in mammals [5]

• RQ simulations are a tool to gain mechanistic understanding of the underlying causes of metabolic flexibility, and to study the link between metabolic health and aging

Results

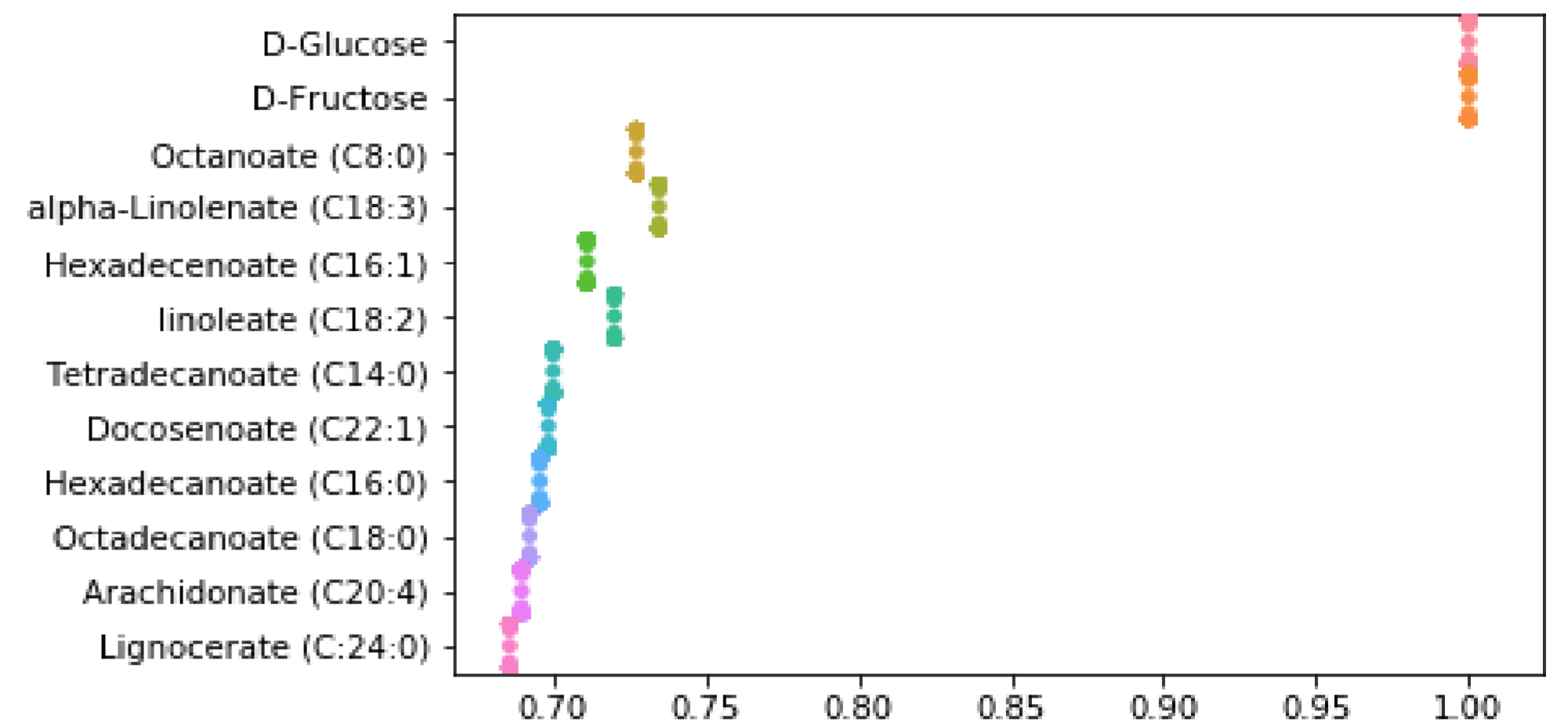


Figure 1: RQ simulated in different individualized models. Each row corresponds to a different carbon source. The model ensemble predictions confirm theoretical RQ values.

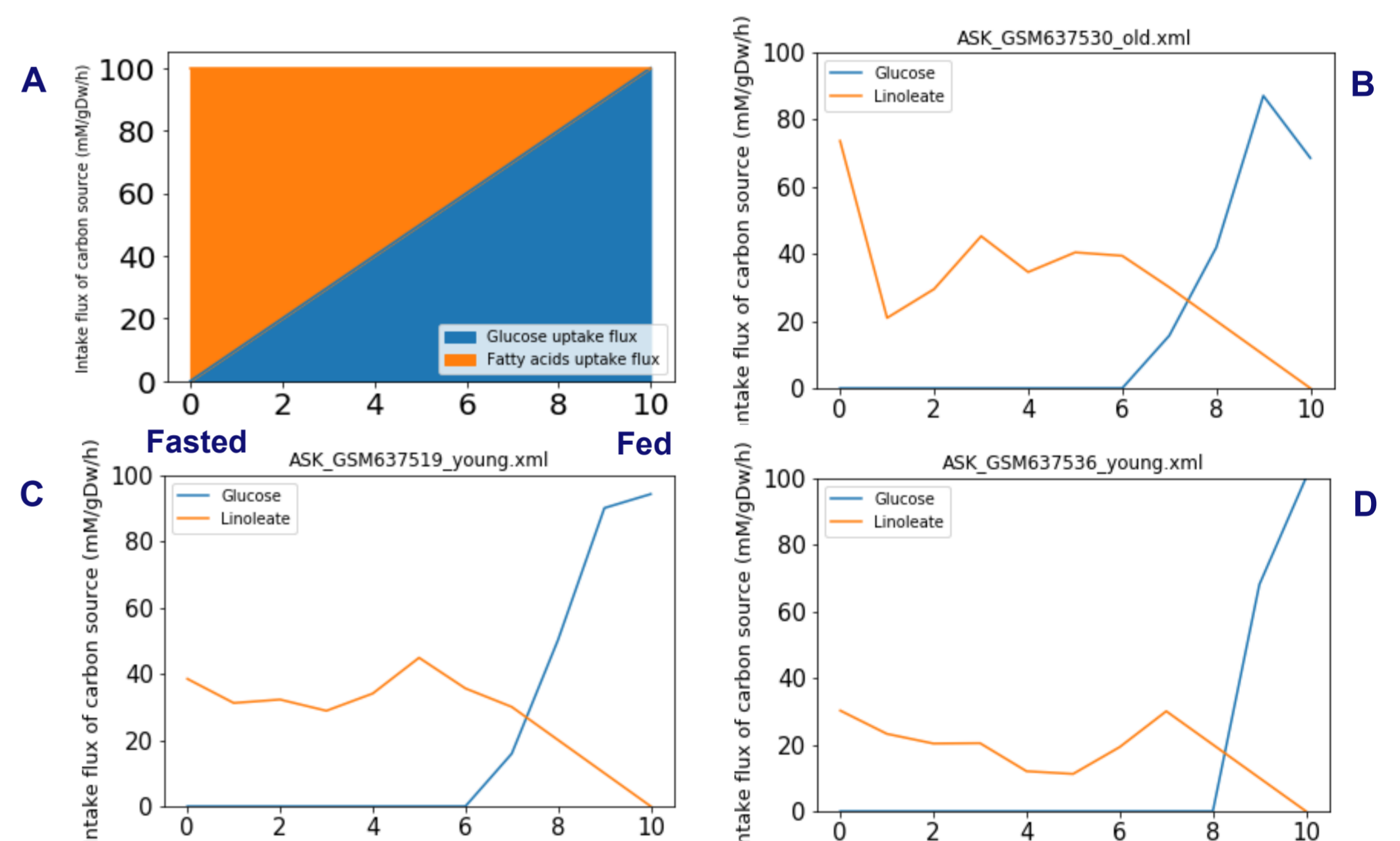


Figure 2: (A) Reciprocal modulation of lipid (CPT1) and glucose (GLUT4) uptake fluxes. (B-D) Different patient-derived models show differential substrate utilization during the fasting-to-fed transition.

Conclusions and Future Work

- The model ensemble correctly simulates expected Respiratory Quotient values when metabolizing different carbon sources
- Results show expected behavior, but also reveal substantial heterogeneity in substrate utilization patterns across patient-derived GSMMs
- **NEXT:** simulate protein synthesis rate in response to different nutrient profiles, to gain mechanistic understanding of the role of nutrition in counteracting muscle loss (sarcopenia) during aging

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