Genome-scale metabolic models for personalized nutrition and healthy aging

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Genome-scale metabolic models for personalized nutrition and healthy aging

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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.

- 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

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

<table>
<thead>
<tr>
<th></th>
<th>Old (n=58)</th>
<th>Young (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Number of Reactions</td>
<td>3331.00</td>
<td>3347.47</td>
</tr>
<tr>
<td>Average Number of Metabolites</td>
<td>2430.22</td>
<td>2434.02</td>
</tr>
<tr>
<td>Average Number of Genes</td>
<td>1234.22</td>
<td>1236.74</td>
</tr>
</tbody>
</table>

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

References