An Integrated COBRA-PBPK Model to Study Interactions between the Gut Microbiome and the Brain in Autism

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Introduction

Autism spectrum disorder (ASD) is a complex neurological disorder causing developmental & social impairments, affecting 1 in 68 people. Recently, gastrointestinal disorders have been reported in ASD, attributed to abnormal proportions of harmful gut bacteria - *Clostridium*, *Bacteroides* & *Desulfovibrio* & reduced beneficial bacteria - *Bifidobacterium* & *Lactobacillus* . Further, intestinal & blood-brain barrier hyperpermeability in ASD results in harmful metabolite exchange between the gut and brain, disrupting neuronal pathways. We develop a novel framework to analyze gut-brain interactions using an integrated COBRA-PBPK model & implement it to understand the ASD metabotype[1].

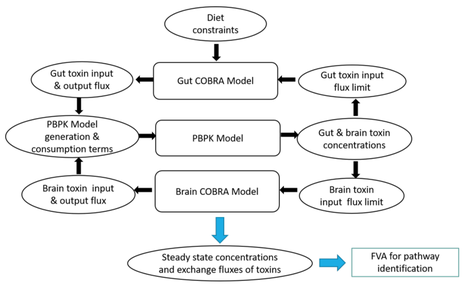

Figure 1: Integrated model construction

PBPK transport model

A physiologically based pharmacokinetic model was built to transport metabolites across 6 tissues of the body - brain, heart, adipose, liver, gut and kidney.

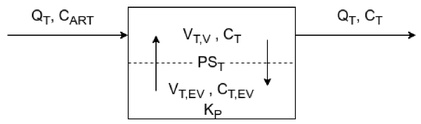

Figure 2: Tissue(T) mass balance modeled with vascular(V) & extravascular(EV) compartments. V-volume; ART-blood; Q-flowrate; S-surface area; P-permeability; K_P-partition coeff.

$$V_{T,V}\frac{dC_T}{dt} = Q_T C_{ART} - Q_T C_T + \frac{PS_T \cdot C_{T,EV}}{K_P} - PS_T C_T$$

$$V_{T,EV}\frac{dC_{T,EV}}{dt} = PS_T \cdot C_T - \frac{PS_T \cdot C_{T,EV}}{K_P}$$

Constraint-based Models

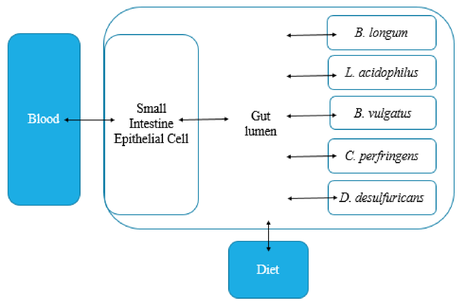

Figure 3: Coupled gut and microbiome model constructed by combining the small intestine model (SIEC[2]) with individual bacterial models of interest (AGORA[3]), allowing for extracellular metabolite exchange through the lumen compartment.

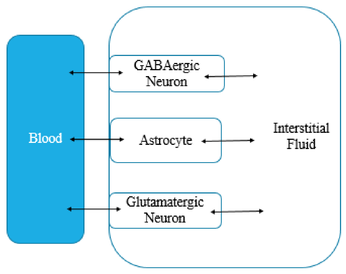

Figure 4: Coupled brain model constructed by combining different neuronal cell models & allowing for interactions [?]

Table 1: Model Statistics

Model	Reactions	Metabolites
SIEC	1282	844
Gut microbiome-Beneficial	3177	2611
Gut microbiome-Harmful	5323	4365
Gut microbiome	7137	6056
Brain	1542	1428

Further, typical autistic and healthy gut microbiome models were constructed using 80:20 proportion of harmful:beneficial bacteria, and vice-versa respectively. This was implemented using a novel pareto-optimality framework described in the next section.

Constraint-based Analysis

- **Weighted Pareto Optimization**: We developed 2 algorithms using linear & binary search, to ensure growth of all species in the gut microbiome model.

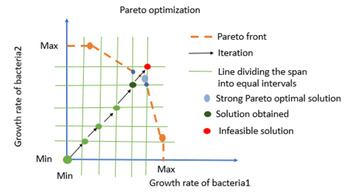

Figure 5: Pareto optimization algorithm

- **Model comparision with FVA**: Flux Variability Analysis was used to define two reaction-wise metrics for model perturbation - mean shift (MS) & range change (RC) .

$$\mathrm{MS} = \left| \frac{\mathrm{FVAMax1} + \mathrm{FVAMin1}}{2} - \frac{\mathrm{FVAMax2} + \mathrm{FVAMin2}}{2} \right|$$

$$\mathrm{RC} = (\mathrm{FVAMax1} - \mathrm{FVAMin1}) - (\mathrm{FVAMax2} - \mathrm{FVAMin2})$$

where, FVAMax1, FVAMin1 - max & min reaction fluxes; FVAMax2 and FVAMin2 max & min reaction fluxes after model perturbation.

Results

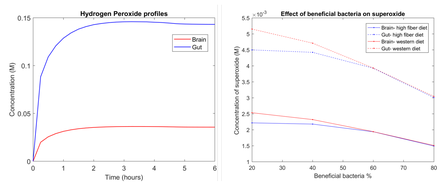

Figure 6: (a) Hydrogen peroxide (molar) profiles under the western diet (b) Effect of probiotics on steady-state superoxide conc.

230 bacterial secretion products were identified, with the top ones linked to autism:

- Toxins - ammonium, propionate
- Oxidative stress & mitochondrial dysfunction metabolites - lactate, pyruvate.

Results

Table 2: Top pathways affected on (a) probiotic addition & diet change to high-fiber (b) increased oxidative stress

Probiotics & Diet	Oxidative stress
Purine catabolism	Oxidative phosphorylation
Propanoate metabolism	Pyruvate metabolism
Pyruvate metabolism	Glutamate metabolism
Vitamin B6 metabolism	Folate metabolism

Conclusions

We developed and analyzed the first-ever quantitative model for autism, finding that:

- Harmful gut bacterial secretions contribute to the autistic metabotype.
- Microbiome & diet mediate nucleotide, central carbon & vitamin pathways in autism.
- Inclusion of probiotics restores gut balance in autism via reduced oxidative stress.

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