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METABOLIC MODELING FOR THE MICROBIOME

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In this talk we will highlight progress in the development of modeling frameworks for describing and predicting metabolic interactions in microbial communities. We will first describe the SteadyCom framework which directly imposes constant growth requirements across all participating microbes present in a stable community. This allows for the quantification of allowable ranges of metabolic exchanges between microbes, predictions for their relative abundance and possible cross-feeding strategies for a given level of growth. Metabolic fluxes are directly linked to overall growth therefore spurious solutions where the organism with the highest biomass yield always dominates the community or non-growing organisms providing carbon substrates to others are avoided. SteadyCom was used to predict abundance profiles, growth rates, and microbial interactions for a variety of communities. Herein we will discuss how SteadyCom was used to explain the spatial and temporal organization of aerobic vs. anaerobic microbes along the length of the human gut. The stable mucosal microbiota was modeled via SteadyCom while the more-transient luminal microbiota was modelled using a dynamic modeling framework. These were allowed to share metabolites and integrated via a population dynamics model linking microbial abundances across the gut. We found that the predicted spatial compositional variations to be consistent with experimentally-measured trends. Sensitivity analysis of simulation parameters revealed oxygen availability per mucosal biomass to be the most significant determinant of the observed spatial distribution. This indicates that computational models can be used to probe the propagation of perturbations in the gut microbiome.

In another effort, we investigated the metabolic activities of the neonatal gut microbiome and systematically tested hypotheses about the metabolic roles of constituent microbes. Using genome-scale metabolic models for six dominant species in the neonatal gut microbiome, we predicted the possible biochemical conversions under aerobic and anaerobic conditions assuming various cellular objectives. We found that the growth of *E. coli* while maximizing ATP yield under anaerobic conditions alone was able to predict the decreased levels of serine, threonine (as substrates for *E. coli*) and increased level of succinate and acetate (as fermentation products) at clinically-observed ratios. These predictions were confirmed in follow-up *in vitro* culture studies where *E. coli* was found to exhibit preferential amino acid use consistent with the predicted patterns. This study suggested that the distal gut of an infant is anaerobic at birth, instead of the prevalent notion of an aerobic-to-anaerobic transition.