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Bugs, babies, and breast milk: a mathematical model

Human milk oligosaccharides (HMOs) are the third most abundant constituent of human breast milk after lactose and lipids, and yet they cannot be digested by infants. A common explanation for the abundance of HMOs is that they preferentially nourish beneficial bacteria, including members of the genus *Bifidobacterium*, in the infant's gut. These bacteria may subsequently grow faster and have a competitive advantage over other, possibly pathogenic, members of the infant gut microflora. Higher abundances of bifidobacteria are associated with health benefits such as disease resistance and vitamin production. Understanding the relationships between HMOs and human gut microflora may lead to advances in neonatal and infant medicine and aid in development of commercial products such as probiotics or infant formula.

A combination of ethical and practical considerations creates challenges in studying HMO metabolism. Direct sampling of gut microflora requires invasive procedures that would be unethical to perform on infants. Additionally, it is difficult to culture many species of gut microflora *in vitro*. For these reasons, researchers currently rely on genetic analysis of stool samples to measure the presence and abundance of microbes in the gut. Unfortunately, these analyses cannot resolve questions about mechanisms. In these situations, insight from mathematical models can help guide empirical work. Thus, the 2011 cohort of trainees in the UC Davis Collaborative Learning at the Interface of Mathematics and Biology (CLIMB) program (supported by the NSF-sponsored UBM program) developed a model of HMO metabolism by the human infant colon bacterial community to investigate the effects of HMOs on the relative abundances of key taxa.

The model consists of 23 differential equations that describe the dynamics of nine microbial taxa and 14 HMOs and HMO constituents. These equations incorporate rates of influx into and efflux out of the gut, microbial interaction with the 14 substrates, bacterial growth from feeding, and crossfeeding, a process in which HMOs are extracellularly degraded by certain microbial taxa with the resulting byproducts available to other taxa. We parameterized the model using time series data of single taxon metabolism of HMOs *in vitro*, and used it to predict the relative abundances of bacterial taxa in a multi-species environment. In order to simulate the natural differences in HMO composition among mothers, we ran our model using different subsets of HMOs. We also tested the effects of preferential feeding on community dynamics by incorporating instances of HMO preference among bacteria.

By simulating the process of HMO metabolism, we successfully predicted the relative abundances of key taxa found in some empirical studies. However, the model does not accurately describe some finer scale dynamics that occur on the order of days instead of weeks. In simulations, differing HMO compositions among mothers and preferential feeding behavior in bacteria each altered the order of relative abundances, indicating that these factors play a large role in community composition. Our predictions can be directly compared to empirical time series data, and the model itself provides a framework for future models. Such models should incorporate other potentially important factors, such as pH of the gut and interspecific competition among members of the gut microflora, in order to test the importance of these factors in determining community dynamics. It is our hope that future models based on this framework will be able to more accurately describe dynamics on the order of hours and days and predict the effects of short term therapies such as antibiotic or probiotic usage.