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An agent-based modeling framework for evaluating hypotheses on risks for developing autism: Effects of the gut microbial environment

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ABSTRACT

The number of cases diagnosed with Autism Spectrum Disorders is rising at an alarming rate with the Centers for Disease Control estimating the 2014 incidence rate as 1 in 68. Recently, it has been hypothesized that gut bacteria may contribute to the development of autism. Specifically, the relative balances between the inflammatory microbes clostridia and desulfovibrio and the anti-inflammatory microbe bifidobacteria may become destabilized prior to autism development. The imbalance leads to a leaky gut, characterized by a more porous epithelial membrane resulting in microbial toxin release into the blood, which may contribute to brain inflammation and autism development. To test how changes in population dynamics of the gut microbiome may lead to the imbalanced microbial populations associated with autism patients, we constructed a novel agent-based model of clostridia, desulfovibrio, and bifidobacteria population interactions in the gut. The model demonstrates how changing physiological conditions in the gut can affect the population dynamics of the microbiome. Simulations using our agent-based model indicate that despite large perturbations to initial levels of bacteria, the populations robustly achieve a single steady-state given similar gut conditions. These simulation results suggests that disturbance such as a prebiotic or antibiotic treatment may only transiently affect the gut microbiome. However, sustained prebiotic treatments may correct low population counts of bifidobacteria. Furthermore, our simulations suggest that clostridia growth rate is a key determinant of risk of autism development. Treatment of high-risk infants with supra-physiological levels of lysozymes may suppress clostridia growth rate, resulting in a steep decrease in the clostridia population and therefore reduced risk of autism development.

Introduction

Although autism spectrum disorders (ASD) have been intensively studied, the causes of ASD remain unclear [1]. It has recently been hypothesized that the composition of the gut microbiome can contribute to the development of ASD [2]. Specifically, Heberling et al. (2013) proposed a Systems Connectivity Model which hypothesized that imbalances between the populations of clostridia, desulfovibrio, and bifidobacteria in the gut may contribute to ASD development [3]. It is possible that imbalances to these bacteria lead to local inflammation and leaky gut, allowing bacterial toxins and inflammatory molecules to reach the brain [3–5]. Studies have shown that individuals with ASD generally have reduced levels of bifidobacteria and elevated levels of desulfovibrio and clostridia [6]. Additionally, some ASD symptoms can be relieved by treatment with vancomycin, an antibiotic aggressive towards clostridia [7].

It remains unclear precisely how the interactions of gut bacterial populations may lead to the imbalanced populations associated with ASD or what treatments may be most promising to correct these population imbalances. Therefore, we advanced the Heberling connectivity model [2] by developing a novel agent-based model (ABM) that simulates the relationship between the pro-inflammatory bacteria clostridia and desulfovibrio and the anti-inflammatory bacterium bifidobacteria during gut microbiome development. The purpose of the model was to develop and test hypotheses where experimental testing could be difficult, time consuming, expensive, or invasive. The current model does not include sufficient detail to act as a predictive tool for patient treatment and was not designed for that purpose.

Although there are many bacterial species present in the gut microbiome, our model assumes bifidobacteria, clostridia, and desulfovibrio are sufficient to create a minimal representation of the

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key features of an autistic gut. We simulate each bacterium as having both direct and indirect effects modulating the growth rates of the others (Fig. 1). Additionally, each bacterium responds to different nutrients available in the gut. Bifidobacteria use glucose, lactose, and fructooligosaccharides as nutrients but are inhibited by lysozymes and increased desulfovibrio populations. Desulfovibrio use chondroitin sulfate and lactate produced by bifidobacteria as nutrients. Clostridia use inulin, glucose, lactose, and fructooligosaccharides as nutrients and are inhibited by lysozymes and high levels of bifidobacteria. As long as other pro- and anti-inflammatory bacteria behave similarly to the bacteria considered in our model, bifidobacteria, clostridia, and desulfovibrio represent archetypal bacteria populations that could be considered as lumped variables representing other species as well.

Hypotheses generation

We used our model as a tool to develop hypotheses about how perturbations to the gut microbiome may lead to unhealthy balances in the population of microorganisms. We tested how initial sizes of bacteria populations could lead to altered population steady-states, how altering dynamics of gut bacteria growth and competition may lead to population shifts, what risk factors may be most indicative of autism development, and how perturbations to population dynamics during the development of autism may correct population imbalances. We hypothesize that bacterial populations robustly achieved the same steady-state despite alterations to initial population balances. We also evaluated the effects of introducing a prebiotic, fructooligosaccharides, into the system and hypothesize that the bifidobacteria population will increase substantially coupled with a slight increase in desulfovibrio and a slight decrease in clostridia. Finally, we hypothesize that lysozymes have a dramatic effect on gut microbiome balances, reducing the levels of clostridia substantially, coupled with a slight increases to the bifidobacteria and desulfovibrio populations. This protective effect suggests treatment with lysozymes or prebiotics as a novel nutritional supplement for infants at high risk for autism development.

Results

Since most of the data available on gut microbe populations is gathered from stool and is relative in nature, we chose to evaluate our results based on shifts from a steady-state rather than exact gut populations. Model simulations were characterized by immediate exponential growth of bacteria followed by a rapid reduction in bacteria levels to achieve a steady-state (Fig. 2A). To retain this developmental behavior while numerically relating the risk for autism to the populations in the model, we propose a quantitative measure called the Gut Bacteria Index (GBI), calculated as follows:

$$\text{Gut Bacteria Index (GBI)} = \frac{[B]/[B]_{ss}}{([C]+[D])/([C]_{ss}+[D]_{ss})} - 1 \qquad (1)$$

where [B], [C], and [D] represent levels of bifidobacteria, clostridia, and desulfovibrio, respectively, and SS represents an average steady-state value for each bacteria (averaged over 1500 time steps after equilibrium was achieved). A GBI of zero means the gut bacteria is in a similar state as the control (Fig. 2B), while GBI > 0 means a lower risk of developing an ASD and GBI < 0 is associated with a higher risk of developing an ASD. As expected, the GBI profile stochastically oscillated around zero during the control condition. Additionally, we found that the population of desulfovibrio in our model was heavily tied to the population of bifidobacteria, which can be explained by the tendency of bifidobacteria to produce lactate, which is an energy source utilized by desulfovibrio (see also Fig. 1) [8,9].

It is reasonable to assume that, during autism development, interactions between clostridia, desulfovibrio, and bifidobacteria may become deregulated altering the apparent growth rate of these bacteria. To simulate this situation, we increased the growth rate of each bacterium and observed the steady-state achieved (Fig. 3). The growth rate increase in reality could be due to any critical variable that was not included in the model. For example,

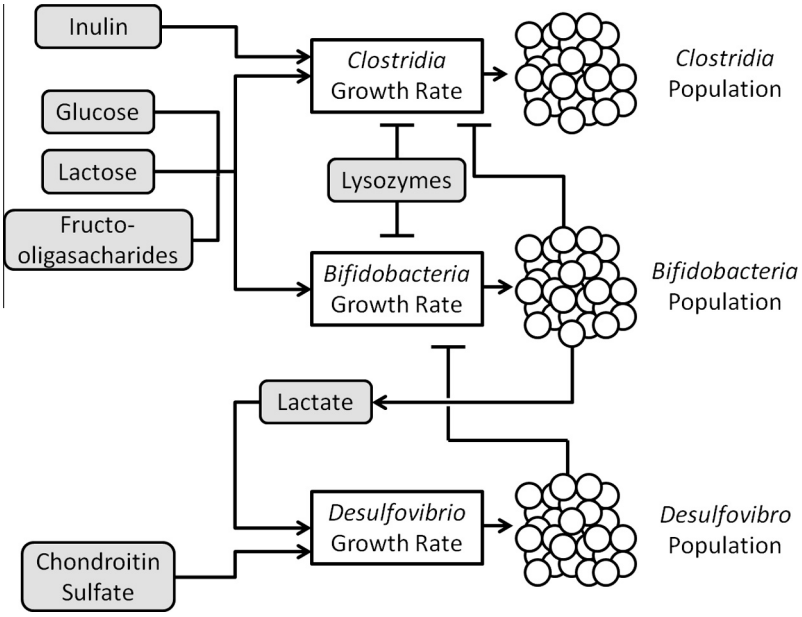

Fig. 1. Conceptual model of gut microbial interactions. Each bacterial population grows in response to specific nutrients. Bifidobacteria inhibits the growth of both clostridia and desulfovibrio, directly and indirectly, respectively. It also, through the production of lactate, induces desulfovibrio growth. Desulfovibrio directly inhibits bifidobacteria growth rate. Clostridia and bifidobacteria indirectly inhibit the growth each other through competition for food sources. Arrows represent positive feedback; flat heads represent negative feedback.