Microbiome: The Allies Within

Project Module Associated with

2nd Edition, Introduction to Computational Science: Modeling and Simulation **by**
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Prerequisite: Knowledge of agent-based modeling, such as obtained through Module 11.2 on "Agents of Interaction: Steering a Dangerous Course"

Introduction

Sharing your body are trillions of microscopic species, primarily bacteria dwelling in your digestive tract (gut). Mixed with the bacteria are other microbes, such as fungi and viruses. Collectively, these organisms are called the *microbiota*, and those in your gut are your *gut microbiota.* We refer to these communities, including their genetic information, as the *microbiome*. Focusing on the bacterial communities in the small and large intestine, we find that most of them act positively within our bodies, benefitting and impacting various bodily functions—immunity, appetite, energy metabolism, and even neurological traits. Recently, some studies have even suggested that the state of your gut microbiota can influence your motivation for doing exercise.

Complex carbohydrate molecules (e.g., certain starches and fibers) are not as easily digested and absorbed by the small intestine, so they are passed on to the large intestine, which contains an enormous number of bacterial species with specialized enzymes that can break down these molecules. Fibers are particularly important, because bacteria of the large intestine can ferment (metabolize) them, producing much smaller molecules, called *short-chain fatty acids* (SCFA's) (see below). The body can use these SCFA's as nutrients, especially for muscle function. SCFA's have already been used clinically to treat irritable bowel diseases (ulcerative colitis, Crohn's disease) and diarrhea following prolonged antibiotic treatment. Furthermore, increased production of SCFA's is linked to reduced obesity for people with high-fat diets and appetite regulation.

Common Short-Chained Fatty Acids and Potential Physiological Roles:

acetic acid – CH_3COOH
- metabolite for bacterial growth
- cholesterol metabolism and lipid synthesis
- possible role in appetite regulation

propionic acid – CH_3CH_2COOH
- regulation of gluconeogenesis (sugar production from non-carbohydrate sources)
- signaling of satiety (fullness)

butyric acid – $CH_3CH_2CH_2COOH$
- main energy source for cells lining the colon
- regulate gut hormones and reduce appetite

Can you think of ways to improve the quality of your gut biota? Scientists have found is that the gut microbiota varies individually throughout each person's lifetime. Besides age, it turns out that your diet may influence greatly the composition of your gut's microbiota and microbiome. Consequently, you may be able to alter the composition and quality of your microbiota by eating more healthily. So, perhaps you need to ditch the processed foods and add more fruits and vegetables, particularly those with significant amounts of fiber, to your diet. In doing so, your microbiota will work for your good health as an ally.

Projects

Parameters and Assumptions for the Models

Assume that the world is an 80-by-25 grid that wraps horizontally. The world models a lengthwise cross-section of the gut with one-fifth being for the mucus above, one-fifth for the mucus below, and three-fifths for the lumen. Movement is from left to right.

Agents include polysaccharides, bacteria (species 1 and 2), and short-chain fatty acids (SCFA), which are acetates, propionates, and butyrates. Allow the user to specify the initial numbers for each of these agents. However, we recommend the following default initial values: polysaccharides:

Agent	Default Initial Value
polysaccharides	800
Bacteria-1	200
Bacteria-2	200
Acetates	600
Propionates	200
Butyrates	200

Also, allow the user to specify the simulation stop time, with a default value of 40 hr.

Initialize agents in random positions in the gut using the following caveats:

Agents are distributed with normal distribution in *y*-direction, so that there is a higher concentration towards the horizontal mid-line. However, in the mucus, they are distributed uniformly. The approximate initial percentages of agents in each part of the gut are as follows:

Agents	Approximate in Lumen	Approximate in Mucus
Polysaccharides	35%	65%
SCFA	95%	5%
Bacteria	45%	55%

Initialize bacteria as follows:

Bacteria should have a random amount of energy. Use a gamma distribution with alpha = 3.04 and lambda = 1.86. For each generated random number greater

than or equal to 4, generate another random energy value. (This distribution was derived from results at 48 hours.)

Have a bacterium be digesting a polysaccharide with probability 0.5%. Approximately 40% of Bacteria 2 that are not digesting a polysaccharide are digesting an acetate. For those bacteria that are digesting, indicate that the remaining time they have to digest is a uniformly distributed random number from 0 to DIGEST-TIME, which is 6 ticks.

Indicate that about 5% bacteria that are not digesting are not searching for something to digest. The remaining time before such a bacterium begins to search for nourishment should be a uniformly distributed random number from 0 to TICKS-TIL-SCAN, which is 60 ticks.

1 tick represents 10 sec.

A person eats 3 times a day, at 6:00, 12:00, and 18:00. Each meal lasts 30 minutes. During that time, a polysaccharide appears at a random position in the gut every 10 sec.

When a person is not eating, a polysaccharide appears at a random position every 50 sec.

40 polysaccharides/hour enter system besides at meals.

It takes 40 hr for materials to go through the gut.

It takes 6 hours for a bacterium, which does not "eat," to lose enough energy to die. Thus, every tick, a bacterium loses 0.0005 units of energy.

It takes 4 units of energy before a bacterium divides; 2 units of energy are used in the process of dividing; the remaining energy is split between the two resulting bacteria. The new bacterium moves away from the parent. A bacterium that is digesting does not divide.

A bacterium that is about to divide does not start to digest a metabolite.

A bacterium only digests one metabolite at a time.

After completing digestion, a bacterium waits 10 minutes before searching for another metabolite to digest.

A Bacterium-1 starts digesting one polysaccharide at the same location with a probability of (1/180)/tick, while a Bacterium-2 starts digesting a polysaccharide in its cell with a probability of (1/330)/tick. If a polysaccharide does not share its location, then a Bacterium-2 starts digesting an acetate there with a probability of (1/1027)/tick.

A bacterium takes 1 minute to digest a polysaccharide or an acetate. After digestion of a polysaccharide, a species 1 bacterium produces a propionate (probability of (5/17)/tick) or an acetate (probability of (12/17)/tick). After digestion of a polysaccharide, a species 2 bacterium produces an acetate, while after digestion of its second acetate, a Bacterium-2 produces a butyrate. Any product is moved away at a random location, two units from the bacterium that produced the SCFA. A bacterium gains an equal fraction of one unit of energy during digestion of a polysaccharide or an acetate.

It takes approximately 40 hr for something (bacteria, polysaccharides, SCFAs) to move through the lumen. However, at each tick, the agent moves an appropriate random amount to the right and tends to move towards the mucus. Being smaller, acetates tend to move slightly faster towards the mucus.

In the mucus, polysaccharides and bacteria wiggle but do not leave the "world." In the mucus, SCFAs are transported to the cell wall for absorption. Transporters and the cell walls are not depicted. Assume that acetates move a bit faster towards the cell wall, which is outside the world.

In a healthy gut, the SCFA should be approximately in proportion as follows: acetates: propionates: butyrates = 3:1:1

Using the above parameters, average number of bacteria of the two species should be approximately the same. However, the average number of Bacteria-2 might be a little higher than the average number of Bacteria-1.

The algorithm is as follows:

Set up
Do the following up to the stop time:
Move
Digest
Convert
Bacteria use energy
Bacteria possibly die
Bacteria possibly divide
Gut possibly intakes a polysaccharide

Projects

1. Develop a microbiome simulation and display the final number of each type of agent. Run the program at least ten times, and have a spreadsheet calculate the average final number of each type of agent.

2. Have your program run the simulation an indicated number of times. At the end of each simulation, store in a file the final number of each type of agent. Run the simulation 100 times. With a spreadsheet or your program, calculate the average final number of each type of agent.

3. Enhance Project 2 by saving an image of the interface at the end of each simulation.

Enhance your project with one of the feedback mechanisms below. For each project, run the simulation a number of times and describe the results as they compare to be base case in Projects 1-3.

4. Bacteria 2 produces a toxin, which eventually can kill it. However, Bacteria 1 consumes this toxin.

5. Whichever bacteria species is dominant produces a toxin that inhibits the growth of the other species of bacteria.

6. The lumen produces a toxin that inhibits the growth of the dominant species.

Enhance your project with one of the antibiotic treatments below. Assume that antibiotics move along the gut lumen. For each project, run the simulation a number of times and describe the results as they compare to be base case in Projects 1-3.

7. Assume both types of bacteria are sensitive to the antibiotic.

8. Assume that Bacteria 1 are more sensitive to the antibiotic than Bacteria 2.

9. Assume that Bacteria 2 are more sensitive to the antibiotic than Bacteria 1.