Can Microbes Encourage Altruism?

If gut bacteria can sway their hosts to be selfless, it could answer a riddle that goes back to Darwin.

By Elizabeth Svoboda

Parasites are among nature's most skillful manipulators — and one of their specialties is making hosts perform reckless acts of irrational self-harm. There's *Toxoplasma gondii*, which drives mice to seek out cats eager to eat them, and the liver fluke *Dicrocoelium dendriticum*, which motivates ants to climb blades of grass, exposing them to cows and sheep hungry for a snack. There's *Spinochordodes tellinii*, the hairworm that compels crickets to drown themselves so the worm can access the water it needs to breed. The hosts' self-sacrifice gains them nothing but serves the parasites' hidden agenda, enabling them to complete their own life cycle.

Now researchers are beginning to explore whether parasitic manipulations may spur host behaviors that are selfless rather than suicidal. They are wondering whether microbes might be fundamentally responsible for many of the altruistic behaviors that animals show toward their own kind. Altruism may seem easy to justify ethically or strategically, but explaining how it could have persisted in a survival-of-the-fittest world is surprisingly difficult and has puzzled evolutionary theorists going all the way back to Darwin. If microbes in the gut or other tissues can nudge their hosts toward generosity for selfish reasons of their own, altruism may become less enigmatic.

A recently developed mathematical model and related computer simulations by a trio of researchers at Tel Aviv University appear to validate this theory. The researchers showed that transmissible microbes that promoted altruism in their hosts won the survival battle over microbes that did not — and when this happened, altruism became a stable trait in the host population. The research was published in *Nature Communications* earlier this year.

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The lancet liver fluke, *Dicrocoelium dendriticum*, spends part of its life cycle in grazing mammals. At an earlier stage, it invades the bodies of ants and compels them to wait atop blades of grass, increasing the chances that a grazing animal will eat them and pass on the parasite. Such examples show the power of some parasites to manipulate host behavior.

"The story is fascinating, because we don't think of altruism in terms of the host-microbiome relationship," said John Bienenstock, a biologist at McMaster University in Hamilton, Ontario, and director of the Brain-Body Institute at St. Joseph's Healthcare Hamilton, who was not involved with the simulation work. "You can't ignore the possible effect of what your bug population is doing."

Even when Darwin was developing his theory that the strongest and fittest individuals in each generation were most likely to control resources and leave progeny, he recognized altruism as a befuddling challenge. "It is extremely doubtful whether the offspring of the more sympathetic and benevolent parents … would be reared in greater numbers than the children of selfish and treacherous parents," he wrote in *The Descent of Man*.

Darwin hypothesized that altruism might survive if individuals' cooperative behaviors gave the group to which they belonged a collective advantage. The entire group's fitness might then trend upward, enabling it to out-compete other groups with more selfish members. That "group selection" model of evolution was developed further by later scientists, and it found powerful advocates such as the leading naturalist Konrad Lorenz.

But in the 1960s, work by influential evolutionary theorists such as John Maynard Smith and George C. Williams dealt a blow to group selection by demonstrating that altruistic traits were hard to maintain in an evolutionary context. Selfish individuals would still appear spontaneously and would tend to have more offspring, edging out more generous members of a species and ensuring the persistence of selfishness.

The biologist William D. Hamilton made an end run around this problem in 1964 by invoking a strategy that Maynard Smith had called kin selection. Hamilton proposed that altruism could persist if helpful individuals' actions allowed family members to pass on enough of their shared genes to compensate for any reduction in the altruistic individuals' own progeny. This principle is laid out in a formula called Hamilton's rule (C < rB), which states that if the cost to a giver (C) is less than the benefit to a recipient (B) multiplied by their genetic relatedness (r), altruism will come to dominate within a population.

Hamilton's rule explains why altruistic behavior evolved among ants and bees, which are famously social insects. Because of quirks of their haplodiploid genetics, female workers share more genes with their sisters than with their own offspring, so it makes competitive sense for them to sacrifice their own fecundity to help their colony queen mother produce more sisters. The relevance to other animals, however, is murkier. (The geneticist J.B.S. Haldane, who explored early concepts of kin selection in the 1930s, is sometimes alleged to have joked that, as a human being, he would lay down his life for two brothers or eight cousins.)

Kin selection is one example of "inclusive fitness" theories that have been advanced to explain altruism since the 1970s. "Multilevel selection" theories that would include forms of group selection have also had a resurgence, championed by biologists such as David Sloan Wilson of Binghamton University, but they remain contentious.

Still, when it comes to altruism, "there are many explanations, but it still sounds like a mystery," said Ohad Lewin-Epstein, an evolutionary biologist and programmer at Tel Aviv University. As a student in the biology laboratory of Lilach Hadany, he took part in research on how cooperation among members of a population can affect the evolution of new traits. The team came to feel that the classical explanations for the evolution of cooperation weren't the whole story. In particular, Hadany and Lewin-Epstein, with Ranit Aharonov, a computer scientist visiting the university from IBM Research, wondered if microbes could manipulate their hosts to encourage them to help others.

The researchers in Tel Aviv wanted to lend context and focus to an idea that had been debated for some time: Can transmissible "piggybacking" factors encourage altruism? In 2013, Sorcha Mc Ginty, a biologist then at the University of Zurich, and her colleagues created a computer model showing that plasmids — genes that move from one bacterium to another — help spur the evolution of cooperation within bacterial communities. In 2015, a group at Paris Descartes University experimentally demonstrated that when bacteria exchange certain plasmids, the plasmids reprogram the recipient bacteria with genetic information that compels them to contribute to the common good. The bacteria secrete proteins that destroy antibiotics in the vicinity — a strategy that protects the entire bacterial community. To Lewin-Epstein and Hadany, results like these raised the question of whether microbes or parasites that move between complex hosts might drive cooperation as well.

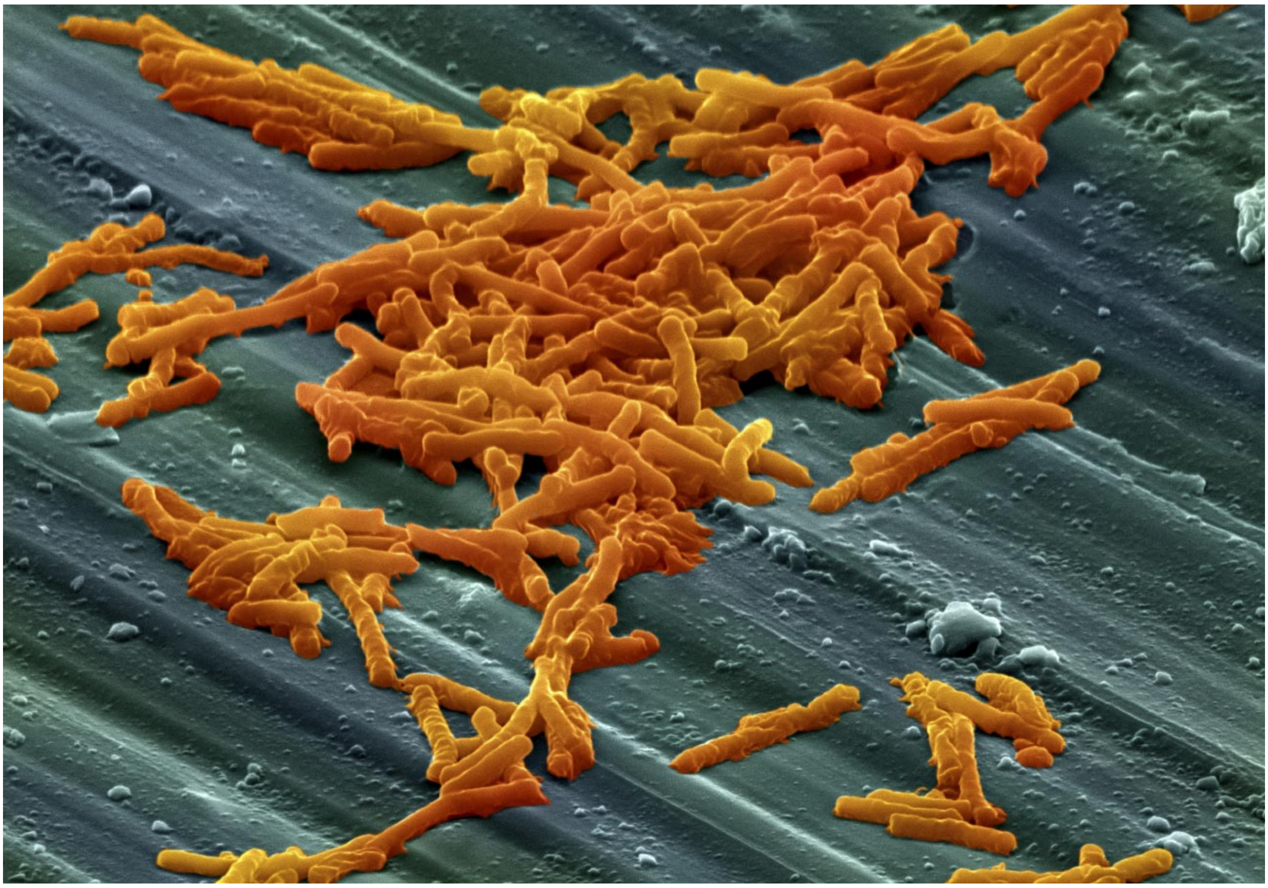
To explore this question in depth, the Tel Aviv group created both a mathematical model and a computer simulation that analyzed interactions among members of a population over hundreds (and in some cases, thousands) of generations. The model assumed that altruistic members incurred some fitness cost when they interacted with others, while the recipients of altruistic acts benefited. The definition of altruism the study uses is broad, Lewin-Epstein says, with costs to the giver that can range from minor to a high degree of self-sacrifice.

The researchers then pitted two types of virtual microbes against each other in the simulation. One microbe promoted altruism in its hosts, while the second did not. In each generation, individuals interacted in ways that allowed both types of microbes to pass from one host to the next, and each individual's microbes were then transmitted to its offspring. Over the generations, microbes that encouraged altruism in their hosts out-competed their rivals when both passed from one host to another and were subsequently passed from parent to child. This was true even when the population of "pro-altruism" microbes was very small at the outset. Pro-altruism microbe recipients were fitter in that they had benefited from another host's generosity, meaning they were more likely to produce offspring carrying the same microbe.

By the end of the simulation, the host population consisted mostly of individuals carrying the altruism-promoting microbe — in some scenarios, 100 percent of hosts ended up with the microbe. That outcome led to the sustained expression of altruistic behavior within the population. A stable level of altruism persisted even when there were selfish hosts in the mix that refused to reciprocate. The mathematical models and simulations also demonstrated that microbe-transmitted altruism ultimately became more stable within a host population than selflessness that had genetic origins.

"Previous works considered altruism only from the perspective of the host," Hadany said. "Where classical models would explain the evolution of altruism under some circumstances, this [could explain the] evolution of altruism under wider conditions." Andrew Moeller, an evolutionary biologist at the University of California, Berkeley, who studies gut microbiomes, said the findings warrant further study. "Microbes can influence the behaviors of animal hosts, so it is not outside the realm of possibility that microbes could promote altruistic behaviors."

Some studies have explored the means by which microbes might control hosts' brain function and social behavior. For example, Elaine Hsiao, a biologist at the University of California, Los Angeles, recently observed that microbes in a healthy colon drive intestinal cells to produce the neurotransmitter serotonin, which then circulates in the blood. Serotonin affects intestinal muscle tone, but it is also the neurotransmitter on which drugs like Prozac act to relieve symptoms of anxiety and depression.



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Some bacterial species in the group *Clostridium* have been found to promote the production of the neurotransmitter serotonin by cells in the intestines. This might in principle be a way for intestinal parasites to influence a host's mental state (although this effect has not yet been demonstrated).

And according to various animal studies, gut flora alter neural and endocrine function in ways that alter hosts' social interactions. In a 2014 study at McMaster University, an animal behavior student, Isvarya Venu, discovered that fruit fly larvae are attracted to airborne chemicals released by the bacteria in their guts; the appealing scent may draw the larvae toward one another. (This manipulation could benefit the bacteria by bringing them closer to new potential hosts.) The connection between a host's microbiome composition and its resulting behavior is known as the "microbiota-gut-brain axis." It's possible, then — though not yet proved — that microbe-produced compounds could influence neural processes that give rise to generous impulses.

Another question raised in the *Nature Communications* paper is whether the presence of altruism-promoting microbes could kick off an evolutionary arms race between microbes and their hosts. It might be in the hosts' best interest, after all, to resist being manipulated by the microbes: Such resistance would mean hosts could keep more resources for themselves, increasing their odds of survival. "If the host has a mutation that makes it resistant to the manipulation of the microbe, the host could start behaving less altruistically," Hadany said.

Yet microbes could respond, she added, by finding new ways to manipulate hosts — or even by striking a win-win deal with them: "A new microbe could evolve, this microbe could spread in the population, and while the microbe benefits, the host also benefits." But regardless of which one benefits more, microbes usually have an edge on their hosts in one major area, she said: "There are many more microbe generations, [so] the microbes have an evolutionary advantage."

If Hadany and Lewin-Epstein's theory holds up, it could have a profound impact on how we approach medical interventions that affect gut microbes. If microbes influence social behaviors such as altruism, doing things that change our microbial balance — such as taking antibiotics or probiotics — could potentially reshape how we treat one another by weakening or strengthening the manipulations that are part of our normal behavior. What would happen, for instance, if one group of subjects was given heavy doses of antibiotics and another group was left untreated? Would the treated group, now rid of microbial manipulators, act more selfishly than the untreated one?

Early experimental results point to at least some connection between antibiotic use and social behavior. When Bienenstock exposed mice to low-dose antibiotics in utero and soon after birth, the treated mice showed lower levels of sociability and higher levels of aggression than mice in a control group — results Bienenstock reported in April 2017. Further studies need to be done to confirm causation, Bienenstock noted, since it's possible the results could be due to the antibiotics' direct influence on the brain or other effects they may have on development. But "the very good chance is that this is an effect on the [gut] bacteria, which are producing materials which in turn are needed by the brain," Bienenstock said. When these biological building blocks are in short supply, he believes, the brain's normal social programs do not function optimally — which could, at least in theory, give rise to more selfish individuals.

But although Bienenstock and his colleagues have looked at how antibiotic use affects mice's social savvy, they have not assessed how antibiotics might specifically affect altruistic behaviors. One logical next step, says Arnon Lotem, a behavioral ecologist at Tel Aviv University, is to create an experiment that assesses whether animals that receive antibiotics show higher or lower levels of helping behaviors. (Lotem is not involved in Lewin-Epstein and Hadany's research.) The study could be run on subjects of various ages to determine whether a potential "selfishness effect" is strongest during certain phases of life. "Maybe nothing will happen — it will just end up as a nice idea that will turn out not to be correct," Lotem said. But if the theory is correct, he added, "it will be amazing."

Hadany and her colleagues are in the process of testing their theory in the lab by evaluating how antibiotics affect the behavior of social insects. "Our general prediction of the model is that treatment that dramatically alters the microbiome might lower [the] tendency for altruistic behavior," Hadany said. She also speculates that interspecies transmission of microbes — from dogs to humans, say, or the other way around — could affect interspecies altruism, another prediction that could be tested using animal models.

If our fundamental decisions about how to relate to others are guided by an unseen microbial cabal, future findings will add depth and complexity to our understanding of generosity. Bienenstock points out that proving the existence of microbial influences on host behavior could upend basic assumptions about the control we have over our thoughts and actions. "Each unitary organism is associated with bacteria, viruses and so on," he said. "You can't look at the altruism without looking at the host." Hadany said her research has transformed her conception of free will. "Any behavior — I'm now thinking, 'Is it me, or is it my microbes?'"

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