

Understanding the microbiome

The microbiome is the term given to the universe of bacteria and other microbes that live in concert with the human body, or with other eukaryotic organisms. Not long ago, biologists viewed bacteria as isolated or atomized agents largely exploiting their hosts through individual action, although a few researchers have emphasized the social skills of some bacteria, such as their ability to hunt collectively (see, for example, J. A. Shapiro, *Stud. Hist. Phil. Biol. Biomed. Sci.* **38**, 807–819; 2007). This view is now more the norm, in part due to the Human Microbiome Project, which has sequenced the genomes of bacteria present in hundreds of distinct people, and begun to reveal the vast complexity of microbial communities.

We're learning that the microbes in our guts act in concert, much like another bodily organ, carrying out tasks that human cells cannot, influencing everything from metabolism to immunity. Biologists are also finding that basic ideas about how organisms interact and fit together in communities need rethinking. The classic theory of biological communities, developed over the past century in the context of higher eukaryotic organisms, rests on the belief that genes descend only vertically, from organisms to their offspring. It also assumes that ecological processes — changes in the populations of different species — typically happen much faster than evolutionary changes, as reflected in altered genes or genetic frequencies, a separation in timescales that simplifies analysis. Microbial communities show little respect for these ideas.

In the microbial world, genes flow freely from one organism to another, even across species boundaries, and bacteria often evolve as fast as their numbers shift through reproduction. Unlike most eukaryotes, bacterial species collectively produce public goods such as protective biofilms, or biomolecules valuable to all species in common. They also routinely re-engineer their environments in more profound ways than eukaryotes do.

A century ago, to understand the microscopic world physicists had to abandon many classical principles, and theorists of biological communities now face a similar challenge. In a beautiful recent review, biologists Britt Koskella, Lindsay Hall and Jessica Metcalf examine the areas where microbial communities break most strongly with classical precepts (*Nat. Ecol. Evol.* **1**, 1606–1615; 2017).

A first casualty is that convenient separation of timescales for eukaryotic communities, where population dynamics play out much faster than evolutionary adaptation. This mismatch implies a simple rule — that the response of a community following some perturbation or shock should be predictable from the evolutionary pre-adaptedness to the new conditions of the various species present. Not so in microbial communities. Researchers have found that microbes often fill empty niches through new bursts of evolution, reconfiguring themselves to be adapted to a new setting. This is found in lung transplant patients, for example.



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Because evolutionary change takes place as fast as ecological change, these two dynamics interact with one another, undermining another tenet of classical theory. This is the expectation that species found coexisting in some environment will not directly compete with one another, but will tend to show distinct capabilities, and rely on non-overlapping resources. This follows because fast ecological dynamics should select out the fitter of two species in competition. In the microbiome, however, many bacterial species often rely on very similar strategies. This means it's hard to identify bacterial species present in a sample just by detecting the presence of genes that reflect a particular function, such as the ability to digest a resource.

Further confusion even in identifying the bacteria present in a microbial community comes from other mechanisms that break the link between function and identity. In eukaryotes, genes flow down hereditary lines and act as unique identifiers of a species. In contrast, microbes routinely spread genes between themselves — so-called horizontal gene transfer — so that detecting a gene becomes useless in identifying a species.

The microbiome also challenges the notion of species as a key organizing concept. Organisms in microbiotic communities often work so well in concert to achieve ends that the boundaries between species dissolve. The anthrax bacterium, for example, releases compounds known as siderophores that scavenge iron from iron-bearing proteins, making this scarce element required for DNA synthesis available to all. Another puzzle: if two or more bacterial species coexist, and thrive by harvesting similar resources, some of those bacteria will often lose some of the key genes they would, naively, require. They can simplify their genomes and rely on the supply of these genes from their closely related neighbours. The species concept loses meaning.

As Koskella and colleagues note, there is one final feature distancing microbial communities from classical ideas. Most organisms influence their environments, and those environments shape them as well. But this interaction is far more dynamic in microbial communities, which typically coevolve with their eukaryotic host. Some human genes of the immune system, for example, act directly to shape the composition of the gut microbiome for specific purposes, favouring some species over others. On a more sophisticated level, some epithelial cells produce microRNAs able to enter directly into microbial cells and regulate their genetic transcription. Hence, the behaviour of a microbial community cannot be understood simply as a spectrum of microbes competing and adjusting within a passive environment.

Thus the microbiome is putting pressure on a range of received biological principles. Given these problems, many biologists hope it might be possible to understand the microbiome by ignoring species altogether, forgetting 'who' is there and looking only at the collection of genes instead, an approach well suited to modern genomics methods. But perhaps we also await new concepts, akin to the ideas of quantum theory, that would at least partially preserve the notion of species and their interactions, and yet also make the strange world of the microbiome more intelligible. □

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