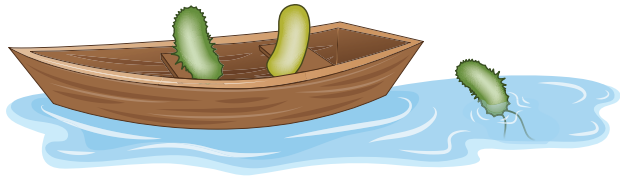
Capturing microbial interactions

New approaches will expose microbial dependencies and environmental interactions.

The science of metagenomics has helped researchers characterize microbes as communities, but we are only beginning to understand the complexities of interactions within these communities and with the environment. The rhizosphere of a single plant root includes commensal and pathogenic bacteria that interact with each other as well as with the plant, soil and fungi. Tumorigenesis has been linked to microbiome-induced inflammation in the gut. Complex interactions such as these clearly have important consequences for agriculture as well as disease and health, and methods are needed for deeper exploration.

A key to understanding microbial ecology and host–microbe interactions will be to develop controlled experimental platforms. Gnotobiotic mice provide a blank slate that can be colonized by different gut bacteria and exposed to various diets for comparative studies. For human environments, organ-on-chip technologies that mimic epithelia and accommodate bacterial culture can also help assess microbial interactions. Combinatorial testing of experimental conditions, such as finding which bacteria need to be cocultured in order to grow, can also help to untangle relationships between individual components.



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Microbial communities define and are defined by their environment.

Sequencing and other omic technologies are effective ways to track microbial composition and metabolic activity, and they allow correlations to be made in the context of well-controlled studies. Sequencing RNA from both prokaryotic and eukaryotic cells simultaneously—in the case of intracellular parasites, for example (*Nature* **529**, 496–501, 2016)—can reveal how host and microbe interact at the level of gene expression. Computational modeling and analysis tools need to be developed to tease out environmental correlations and to understand microbial dependencies and coevolution.

Other *in situ* methods can also help to capture microbial interactions. Techniques for quantitative imaging of labeled bacteria and their surroundings (*Cell Host Microbe* **18**, 478–488, 2015), including fluorescence *in situ* hybridization labeling of bacteria and noninvasive imaging of extracellular milieu components, add a critical spatial dimension to microbial studies. Metabolic labeling and other methods that can track microbial activity will likewise provide benefits.

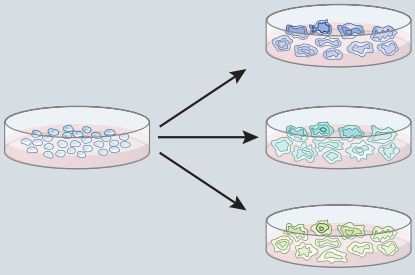
New approaches to understanding microbial interactions should help to solve longstanding and emerging questions, such as how microbiomes can protect against pathogenic bacteria. **Tal Nawy**

Organoid culture

Ex vivo organoid culture could revolutionize biology, but variability must be understood.

Imagine if biologists did not depend upon two-dimensional (2D) culture of transformed cell lines on glass or plastic and could instead study cellular processes in a more realistic *ex vivo* context. The day when this is widely a reality may not be too far off, given the explosive interest in the culture of organoids.

The term 'organoid' is used nowadays to describe *ex vivo* multicellular fragments that contain the major cell types of a particular organ and approximate its *in vivo* organization. They are typically generated by culturing multipotent or pluripotent stem cells in a three-dimensional (3D) matrix (most often Matrigel) under conditions that permit or promote self-organization of the cells. These conditions are determined experimentally but are often informed by prior knowledge of the signals that drive development or regeneration.



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There are now many methods to form different types of organoids.

Organoids have been reported for a range of tissues—retina, kidney, intestine, stomach, lung, brain, and liver, to name just a few. As interest in the technology grows, research efforts are geared toward improved maturation, even to the point of attempting to integrate immune cells and blood vessels into the structures. Increasingly, researchers are also growing organoids from primary tumors, either as models for tumor biology or as a more realistic system for *in vitro* drug screens.

These developments are important. But the technology will stand or fall with the ability to understand variability in the outcomes, correct for it, and ideally control it. We already know from work with differentiating pluripotent stem cells in 2D that factors inherent to a cell line can contribute to variability. This is likely to only be compounded when growing more complex 3D self-organizing structures, for which even quantitative measures of correct structure and function are still being defined. Work geared toward improved control of the process, such as with defined matrices, will be important, as are attempts to understand organoid formation using the arsenal of research techniques—gene editing, imaging—now available to biologists.

The very origins of cell culture lie in 'tissue culture', in attempts to grow out cells from tissue explants. With a return to methods for growing self-organizing organoids, tissue culture has come full circle. But close attention to variability and the development and use of quantitative methods to characterize these structures will be necessary if organoids are to fulfill their potential as *ex vivo* systems for the study of cellular and developmental processes. **Natalie de Souza**