The Chemistry of Microbiomes

Deciphering the chemical signals microbes send to each other could lead to transformative scientific advances. But traditional boundaries between scientific disciplines such as chemistry and ecology have hampered the ability to advance methods for pursuing far-reaching research questions about the complex microbial assemblages known as microbiomes. In a recent seminar series, chemists, biologists, ecologists, and other researchers joined forces to consider challenges and opportunities in the quest to understand the chemistry of microbiomes.

Research in recent decades has brought a radically new appreciation for the role of microbes in our lives. Like people who share a city, the microbes living within microbiomes often have close relationships with their neighbors. While some members of a microbiome may compete or fight with each other, others work together in symbiotic partnerships. Many exchange food or waste products, helping the community as a whole make the most out of limited resources.

At the heart of all of these activities is chemical communication, the universal language that allows the members of a microbial community to function together. While scientists know that chemical signals are crucial to microbiomes, we have yet to fully understand how these signals work. To explore advances, opportunities, and challenges toward unveiling this “chemical dark matter” and its role in the regulation and function of different ecosystems, the National Academies of Sciences, Engineering, and Medicine through the Chemical Sciences Roundtable organized a series of four seminars in the autumn of 2016.

The purpose of the seminar series was to advance opportunities for transformative scientific breakthroughs by amplifying the impact of research on the chemistry of microbiomes. The first three seminars focused on specific ecosystems—Earth, marine, and human—and the last on all microbiome systems. In all seminars, researchers working in a variety of biological systems and environments shared knowledge, identified commonalities and

What is a microbiome?

Microbiome simply means a collection of microbes. Bacteria, viruses, fungi, and other single-celled organisms are found in nearly every organism and environment on Earth. The collection of microbes found in a given environment or organism is called its microbiome; for example, the microbial community found in soil is known as the soil microbiome and the collection of microbes found in the human gastrointestinal tract is called the gut microbiome. Microbiomes are the focus of active research because scientists believe they play an important role in the health and functioning of ecosystems and individual organisms.
opportunities for collaboration, and discussed gaps and challenges.

**OPPORTUNITIES AND CHALLENGES IN MICROBIOME RESEARCH**

Microbiome research represents an incredibly broad field; scientists are studying microbiomes in a variety of organisms and environments, posing a wide range of research questions, using a variety of scientific techniques, and working from the perspectives of many scientific disciplines. There is a particularly wide gulf, for example, between the scientific methods and approaches used in chemistry and the microbiome research questions being pursued from the angle of ecology. Nonetheless, panelists found they shared both opportunities and challenges in common. By promoting collaborations to bridge disparate disciplines, environments, organisms, and approaches, panelists discussed how the field might address some key barriers and foster new breakthroughs.

**ACCURATE GENOME ANNOTATIONS**

An organism’s genome can reveal a lot about the chemical signals that organisms can produce. Information about the functions of specific genes is known as “genome annotation.” Although there are many tools to analyze the genomes present in a microbiome in order to identify the organisms it contains, scientists are still limited in their ability to decipher the specific functions those genomes encode. This lack of accurate genome annotations hampers our ability to understand how individuals collectively work together through chemical interactions with each other and their environment. Expanding our libraries of genome annotations would improve scientists’ ability to investigate the chemicals produced by individual organisms and the signals exchanged among entire microbiomes.

**CHARACTERIZING SECONDARY METABOLITES**

*Metabolites* are chemicals an organism produces during *metabolism*, a collection of processes cells use to stay alive. Scientists have identified about 95% of the primary metabolites in microbiomes. These are the chemicals that are directly involved in an organism’s development, growth, or reproduction. But scientists have only identified about 3–5% of secondary metabolites. While secondary metabolites are not directly involved in sustaining a cell’s life, they are extremely important to a microbe’s ability to communicate. Identifying secondary metabolites is like learning words in the languages of microbiomes; the more words we learn, the better our ability to eavesdrop on microbes’ secret conversations.

Developing a comprehensive catalogue, or dictionary, of secondary metabolites would benefit the entire microbiome community. As a model for such an effort, panelists pointed to the Human Genome Project, suggesting that new technologies would likely make metabolite characterization increasingly faster and more efficient as the project gains steam. In addition to identifying metabolites, panelists also emphasized the value of tracking changes in the abundance of certain proteins, measuring chemical fluxes within and between cells, identifying how the uptake of chemicals changes in different environmental conditions, and advancing chemical and computational models to better understand how all of these chemicals and processes combine to form microbial words and sentences.
MODEL MICROBIOMES

Life on Earth is incredibly diverse. Because this diversity can introduce an infinite number of variables, researchers often develop organisms or biological systems that can serve as “models” to use in scientific investigations. These models are meant to be living examples of a given organism or system that can be replicated many times across different experiments, thus limiting the number of variables that change from experiment to experiment.

There are currently no model microbiomes, which makes it hard for microbiome researchers to compare the results of studies conducted at different times or in different laboratories. In fact, scientists do not even currently have a common way to define a given microbiome, so a gut microbiome studied in one laboratory could be quite different from the gut microbiome studied in another.

Panelists suggested that developing and sharing model microbiomes could help advance the ability to discern the functions of genes, trace the chemicals produced by various microbes, and ultimately decipher the chemical interactions at work in these communities. It would be particularly helpful if these model microbiomes could be informative across systems, allowing them to be used to test hypotheses about microbiomes in different organisms and environments. To develop a model microbiome, panelists suggested looking first to those microbiomes that have been most closely studied so far, since we already have a considerable body of knowledge to build upon. Examples of potential candidate systems include the human gut microbiome, the soil microbiome associated with a model plant, the marine coral microbiome, or the microbiomes found in areas of open ocean with low levels of nutrients.

An important caveat, however, is that while model systems are highly valuable for advancing research, they are not an all-encompassing solution. They represent a simplified version of what’s found in the real world, so it would still be important for scientists to study the broad diversity of natural microbiomes even if model microbiomes become available.

GROUNDING OUR UNDERSTANDING OF FUNCTION

Another major challenge is to understand the true function of microbiomes within their native habitat. Working in the laboratory, scientists can gain valuable insights into microbiome functions by sequencing genomes, cultivating microbial communities, and perhaps developing model microbiomes. But these types of computational and lab-based work are not always representative of what goes on in real-world microbiomes, which involve a complex array of interactions that occur in the context of larger ecosystems. For example, consumer-prey interactions occur simultaneously with carbon and nitrogen processing in complex ways that are not readily reproducible in the laboratory. While model microbiomes could be powerful investigative tools, it remains important to connect what is learned in the laboratory with what is taking place in the actual environment.

LEARNING FROM EXPERIMENTAL ECOLOGY

To better ground microbiome research in the context of the real-world environment, panelists suggested looking for lessons from the field of experimental community ecology. This field has developed research methods that allow insights into the fundamental processes at play in complex systems such as forests and corals; many of these research methods and fundamental processes may also apply to microbiomes. Traditionally, the field of microbiology has focused on investigating individual organisms that can be cultivated in the lab, but such investigations have not generally been very useful for predicting how organisms would interact in nature. Merging techniques and models from lab-based microbiology with those from community ecology in concert with genomics, chemical ecology, and other fields would help to yield a more comprehensive understanding of how microbiomes function.

UNRAVELING COMPLEXITY WITH AN ENGINEERING APPROACH

Incorporating elements of an engineering approach could also help scientists better understand the chemistry of complex microbiomes. In many cases, it will not be practical or even possible to understand all the details of how complex microbiomes function. But if these systems can be teased apart into fundamental components and studied “from the bottom-up,” it may be possible to gain important insights about the overall system based on information about its components. For example, scientists could combine experiments and models to identify and re-create simpler interactions (reducing or ignoring the more complex interactions) between organisms in a microbial community to gain a basic understanding of the “design rules” underlying chemical interactions in microbiomes more broadly.

NEW RESEARCH CAPABILITIES

The scale at which current scientific methods are able to probe the interactions between organisms does not match the scale at which those interac-
tions occur. Because microbes are small and have a high surface-to-volume ratio, each microbe is highly dependent on and responsive to the chemical and physical conditions immediately surrounding it. This means that there will be considerable variation in the activities of microbes within a community, even if that community is cultivated under steady, consistent conditions in the lab. However, methods commonly used to study the chemical dynamics of cells often use hundreds to millions of cells at once to measure genes, transcripts, proteins, and metabolites. The results of such methods reveal population averages, but not the dynamics of individual organisms.

Panelists suggested that more sensitive, high-throughput single-cell techniques are needed to study microbiomes at fine spatial and temporal resolutions. In concert, new computational tools are needed to analyze this data in a statistically robust manner. Measuring the chemical dynamics of a microbial community and computationally combining that data with information about the activities of single cells could allow scientists to analyze the interactions between organisms at the extremely fine scale that those interactions occur.

**THE NEED FOR A COLLABORATIVE APPROACH**

Understanding the chemistry of microbiomes is simply too large a challenge for any single funding institution; it will take a large cooperative, collective effort to understand not only what is happening within microbiomes, but how it happens. Many seminar participants noted the importance of collaboration—not only among scientists, but among funding agencies—for transforming microbiome research from an observational and descriptive science to one that is predictive and based on known mechanisms and principles.

Common tools and technologies can bring communities together and accelerate progress. Participants suggested a useful goal for the microbiome community could be to have, within 5–10 years, a set of fundamental principles that fit within a theoretical framework to explain the assembly and function of microbiomes. Such an achievement, panelists and participants suggested, is likely only achievable through a collaborative approach among diverse research teams and funding organizations.