GENERAL AUTOMATION LAB TECHNOLOGIES

Microbiome Research Demands New, Scalable Tools

Remarkable progress in microbiome characterization has revealed that microbial communities — whether buried under the ocean floor or nestled within our intestines — are even more biologically complex and consequential than expected. Metagenomic studies have shown that the microbial content in soil has significant implications for the growth and pest-resistance of crops. Human health studies are continually uncovering new associations between our microbiome and disease, such as recent findings that microbial populations influence the fate of certain cancers or that adjusting the makeup of a patient's gut microbiome can reduce the severity of autism symptoms.

> Development of accessible, high-throughput tools for characterizing microbiomes easily and cheaply at multiple scales for medical, agricultural, environmental, and industrial uses...will enable small and large laboratories to contribute to and ultimately benefit public health, agriculture, and our economy.
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> Microbiome Interagency Working Group Strategic Plan 2018

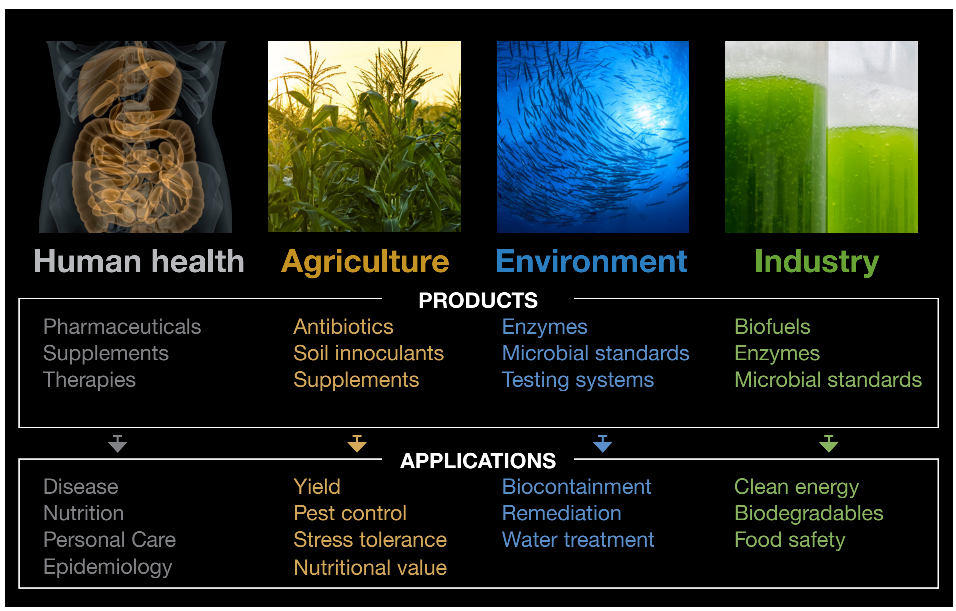

Fig. 1. Examples of current commercial applications resulting from microbial research

Each new microbiome discovery has reinforced the key concept that scientists must be able to parse the full complexity of these communities in order to truly understand their function. It's not enough to catalog the strains present. Unraveling these complex populations also requires determining what each constituent strain does and how they interact with the others and their environment, because those interactions have important biological ramifications. Unfortunately, this is where current technology falls short.

Although progress in characterizing microbial populations has been remarkable, the research community still needs enabling technology to provide a deeper understanding of the interactions within them. Much of microbial research still relies on century-old techniques for core workflows such as culturing, which currently takes too long and fails to accurately represent rare or slow-growing microbes because they tend to be overtaken by more numerous and faster-growing strains. Newer approaches, such as next-generation sequencing (NGS), allow for rapid identification of microbes but lack the ability to elucidate functional properties, such as biochemistry and physiology, and interactions. The ideal solution to this challenge would be a cost-effective, high-throughput tool for microbial isolation and cultivation that would facilitate the isolation and analysis of thousands of strains at once while simultaneously preserving them in living form for downstream functional studies.

Technical Limitations

Today's microbiology labs lean heavily on labor-intensive tools developed in the 19th century. Petri dishes, agar plates, and broth cultures are tried-and-true helpers for confirming the presence of microbes as well as for cultivating them to prepare for downstream identification protocols. These tools are challenged, though, by rare or slow-growing microbes. In culture, abundant and fast-growing strains rapidly outcompete others in a population, making it difficult or even impossible for scientists to spot the less populous members. Slow-growing microbes, which may contribute significantly on a biological level, can have such a long doubling rate that they simply cannot be grown with traditional culture methods.

Beyond their shortcomings with hard-to-culture microbes, conventional tools also suffer from their origins in a 19th-century mindset — one that found it sufficient to determine whether microorganisms existed in a sample, or at most to identify an individual strain. They were never intended to enable the analysis of complex microbial communities with functions beyond that of any single member. Modern demand for characterizing entire populations of microbes cannot be addressed with such antiquated tools.

In the genomics era, many scientists have skipped past the time-intensive culturing step, preferring instead to apply high-throughput NGS technologies. Many of the recent revelations about microbiome biology have been based on NGS analysis of DNA or RNA, which has been quite helpful in allowing researchers to identify multiple strains present in a sample. The approach has been particularly useful in cataloguing differences between, for example, microbiomes associated with health or disease.

However, NGS tools cannot fully characterize microbial communities. DNA-based data cannot provide a clear view of how microbes interact, or of their functions separately and together. Sequence analysis offers only one dimension of the many needed to accurately represent the biology of these complex populations. When something interesting is found in the NGS results, follow-up analysis depends on the ability to go back and study the living strain. But without culturing these organisms, that is not possible. For example, when NGS results indicate that a microbiome is associated with a disease state, there is no way to query those results further to find out whether that relationship is causal or not.

Metaproteomics, or mass spectrometry-based proteomic analysis at the community level, has also been used to glean insights into the workings of these microbial clusters. Unfortunately, this is not a practical solution for a number of reasons. There may be thousands of species present, confounding the ability to link each peptide found to a specific organism. Protein identification is limited to peptides that have already been seen and entered in spectral databases, making it that much harder to characterize the novel proteins expected in a microbial population. And, of course, microbiome samples may be contaminated with proteins from the host.

Innovation Required

The ideal approach to characterizing microbial communities would make it possible to study the biology of these organisms and their interactions. To do that, a major technical breakthrough is needed for high-throughput isolation and cultivation. This would enable researchers to interrogate living strains, performing genomic, proteomic, metabolomic, and other analyses but always being able to go back to the living organism to study phenotype, function, and other core aspects of the biology of these organisms.

For optimal utility, this high-throughput isolation and cultivation system would have to separate microbes from each other to prevent the fast-growing members from overtaking the slow-growing or rare species. This would have to be feasible on a grand scale, since there can be hundreds or thousands of microbial strains present in a community and each one must have the opportunity to be cultured. Also necessary: a streamlined, largely automated workflow to minimize the amount of hands-on time required by scientists or lab technicians.

With this type of platform, researchers could go well beyond today's strain-cataloguing efforts to the much-needed work of elucidating the heterogeneous phenotypes and functions of the microbial players in each community. This will make it possible to generate hypotheses through metagenomic studies and then study and validate those hypotheses using living biological systems, driving real insights and an actionable understanding of mechanism.

Microbiome Applications

The potential reward from a deeper understanding of these microbial communities is incalculable, in part because there are gains to be made in so many different areas.

In agriculture, researchers are struggling to address the issue of how to feed a human population expected to reach 9 billion by the year 2050. The last revolution in agricultural yield was delivered by a combination of genetic engineering, chemistry-based interventions, mechanization, and improved crop management; the next one may very well come from influencing microbial communities living in the soil or on the crops themselves. Multiple studies support the idea that certain microbial populations within soil are associated with greater crop yields, while others indicate that some plant microbiomes are responsible for conferring pest resistance.

When it comes to the environment, microorganisms are known to help regulate climate change due to their roles in carbon and nutrient cycling. Many scientists believe that microbial communities will be important in helping to reduce the environmental impact of climate change and have called for new studies to determine how best to proceed.

Microbiomes are also known to influence human and animal health, although there is a strong sense within the scientific community that we are only just beginning to understand the true impact of these relationships. The recently completed Integrative Human Microbiome Project, for instance, funded deep dives into microbial communities associated with pregnancy and preterm birth, inflammatory bowel disease, and type 2 diabetes. In all cases, microbiomes were found to be significantly influencing human health. Other studies have shown that microbial populations have implications in drug response, cancer progression, autism symptoms, and many other health conditions that would not be intuitively connected to microbial life within us.

> *"What I would like to do is to manipulate microorganisms on a large scale. I want to see how microbes respond to environmental perturbation, how they change in the presence of other organisms, and how they respond to cause a reaction in the host."*
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> *— Karsten Zengler, Ph.D., Associate Professor, University of California, San Diego*

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Prospector™ high-throughput microbial isolation and cultivation system

Prospector microbial isolation and cultivation array

The Prospector System

GALT, a leading developer of next-generation cultivation platforms for microbiome research and microbial product development, has released a microarray-based platform that enables scientists to cultivate target microbes from complex samples using a massively scalable, easy-to-use workflow. The Prospector™ system improves and streamlines the capability and capacity of today's microbiome research and development labs to screen, isolate, and analyze difficult-to-culture or less abundant microbes for high-impact applications in human health, agricultural, industrial, and environmental sciences.

The Prospector system uses microfabricated arrays containing thousands of nanoscale chambers for isolation and cultivation. When a microbial sample is loaded, individual microbes self-sort into the chambers, which are designed to support growth into single-strain microcolonies. A single array has the sampling power of hundreds of culture dishes, allowing researchers to grow thousands of microcolonies in parallel.

With this previously unimaginable throughput, researchers can now ask questions about microbiomes that were never feasible before — and ultimately get results that will make it possible to harness the untapped potential of these complex microbial communities.

Find out more about how high-throughput, scalable, and parallel microbial isolation can benefit your microbiome research studies.

FOR MORE INFORMATION OR TO CONTACT US PLEASE VISIT WWW.GALT-INC.COM

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