Tackling the Microbiome

MICROORGANISMS REPRESENT THE MAJORITY OF LIFE ON EARTH, POPULATING A WIDE RANGE of niches on its surface, underground, in the oceans, in the atmosphere, and both on and inside all multicellular organisms. This “microbiome” will clearly play a critical role as humans struggle to deal with society’s major challenges—health care, agriculture, energy, and the environment. As one example, the human gut microbiome contributes 36% of the small molecules that are found in human blood, and it also plays a major role in creating susceptibility to certain human diseases. In recent years, a variety of microbial communities have been characterized through such efforts as the Human Microbiome Project and the Earth Microbiome Project. But mapping these trillions upon trillions of microbes and analyzing the vast amounts of data that are accumulating will require new integrative approaches aimed at understanding how microorganisms function and are interrelated.

What can individual microbes do? How do communities of microbes interact together to modify their environments? How can we redesign microbes and their communities to have them execute the chemistries that humans need to meet the grand challenges of society? Systems biology offers a powerful approach to framing and experimentally approaching such challenges. There is a multiscale hierarchy of biological information—DNA, RNA, proteins, networks, cells, organs, individuals, populations, and finally ecologies that each contribute to the integrated biological “network of networks.” Dynamical biological networks capture, transmit, and integrate various types of information to the molecular machines inside cells that execute the functions of life and create phenotypes. The structured interactions among members of the microbiome and their interactions (with a host, in some cases) add complexity to these information-processing networks. A systems approach can define these networks, determine how they are interconnected, and follow their dynamics with the goal of understanding how they contribute to phenotypes at all levels.

At the single-cell level, “omics” analyses—genome sequences, epigenetics, transcriptomes, proteomes, non–messenger RNAomes (where relevant), metabolomes, interactomes, phenomes (visual and biological), and omics dynamics in response to environmental signals—will delineate discrete or “quantized” subpopulations of microbes representing populations with distinct functions or the successive stages of a functionally transitioning population. The properties of interacting communities must then be integrated with the behaviors of single cells, individual quantized populations of cells, and the bulk population.

Much fundamental information is still missing. It is striking that more than 60% of the proteins defined by genome analyses have unknown functions. Homology analyses at the three-dimensional level (in silico protein folding) may be a powerful aid, especially when combined with systems approaches that can suggest gaps in the biomolecular networks needed to carry out observed physiological functions. The ultimate goal is to convert data into knowledge—integration of data into appropriate metadata structures (e.g., the “network of networks”)—to generate the predictive models essential for understanding how microbes function. From there, it may be possible to reengineer microbial genomes to make them execute the chemistries that we desire. There are two strategies—a hunt-and-peck method modifying one or a few genes, or the systems redesign of the networks to capture subtle regulatory interactive effects. The latter approach will be greatly accelerated by computational approaches designed to automatically reconstruct provisional metabolic and regulatory networks for isolated species from high-throughput data. Ultimately, it should be possible to reengineer the genomes of microbes in communities to make them function together to execute useful chemistries. For success, academic and industrial research institutions will need to create the focused, integrative, milestone-driven, and cross-disciplinary environments in which transformational systems-driven innovation of metabolomes can thrive.

– Leroy Hood

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