

## Understanding Microbial Genomes

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## Understanding Microbial Genomes

Genome sequencing projects completed over the past few years have revealed unimagined genetic diversity in the microbial world. To capitalize on its investments in these projects, the Department of Energy (DOE) in 2002 created the Genomes to Life program—now renamed Genomics:GTL—to link genomics and computational science in the formidable task of deciphering the fundamental biology underlying all microbial life.

In a road map released in October 2005, DOE outlined plans to merge microbial DNA sequencing with high-throughput biological studies and computational models. Genomics:GTL's ultimate goal is to master microbial biochemistry and physiology so well that scientists will be able to predict microbial behavior in different environments based solely on genome sequence. With this knowledge, they will be able to develop microbe-based strategies for DOE interests like clean energy, bioremediation, and climate change control, says Aristides Patrinos, associate director of DOE's Office of Biological and Environmental Research.

"Computational science is the hope for integrating across knowledge in a way that you can say something predictive," says Grant Heffelfinger, deputy director for materials science and technology at Sandia National Laboratories in Albuquerque, New Mexico. Heffelfinger uses computational methods to study how protein complexes bring ocean carbon dioxide into *Synechococcus* cyanobacteria cells and convert it into sugar. Understanding this fundamental part of Earth's carbon cycle may help scientists devise ways to control atmospheric carbon dioxide released during fossil fuel consumption, he says.

Many GTL-funded scientists study microbial species that hold potential for bioremediation. They study gene expression, protein dynamics, and metabolic reactions in the lab, and then use this information to design computational

models that predict how microbes will function in varying environments—for example, with a different pH, salinity, temperature, or nutrient concentration.

Derek Lovley, distinguished professor of microbiology at the University of Massachusetts–Amherst, is studying species of *Geobacter* that convert soluble uranium into an insoluble form that precipitates out of soil. "We can't possibly go to every site before deciding on a bioremediation strategy," Lovley says, so he and his coworkers are creating computational models that will eventually tell them how to alter conditions or genetically engineer the bacteria to convert uranium more efficiently.

*Geobacter* can also produce energy from waste by oxidizing organic matter and transferring electrons onto an electrode. The bacteria create energy extremely efficiently, but also extremely slowly, so Lovley is feeding high-throughput data into computer models that will predict how to get the microbes to work faster.

Models that allow this level of understanding will rely on development of technologies in biology and computing that don't yet exist, Patrinos says, and the Genomics:GTL program has laid out four "very ambitious but very strategic goals" for developing these technologies.

The first three involve basic microbiology: characterizing the genes, proteins, and multiprotein complexes that govern microbial life; figuring out how these complexes interact in regulatory networks; and determining the molecular basis of interactions in communities such as biofilms. The fourth goal is to develop computational methods to analyze these data and to predict unknown microbial functions.

Much of Genomics:GTL research and development will take place at four core research facilities funded by DOE. Patrinos says that DOE will soon issue requests for funding proposals for the first facility, which will produce and characterize proteins. The other facilities will

focus on molecular complexes within cells, proteomics, and cellular systems and community dynamics. Eventually, these facilities will lead high-throughput study of microbial systems in much the same way that designated sequencing facilities have led high-throughput genome sequencing, Patrinos says.

All labs involved in Genomics:GTL adhere to strict protocols that ensure quality control and reproducibility, says Adam Arkin, assistant professor of bioengineering and chemistry at the University of California–Berkeley, which means that biologists will be able to compare results across different types of data. Arkin's lab is combining data on gene expression, protein interactions, and metabolism in the sulfate reducer *Desulfovibrio vulgaris* to try to "get some idea of the cross-talk between pathways."

Creating open-access online databases is also a big part of the project, says Michelle Buchanan, associate laboratory director for physical sciences at Oak Ridge National Laboratory in Oak Ridge, Tennessee. She is developing high-throughput methods to analyze protein–protein interactions in microbial cells, and her results will be deposited in databases that other scientists can access and annotate with their own research results. Other GTL scientists will create similar databases for metabolic pathways, regulatory networks, and community interactions.

The timeline for realizing specific biological or computational goals is "very sketchy [since] this is a basic science program," says Patrinos, but "we have already accomplished some early successes."

Microbes' potential to contribute to technological innovation in the 21st century is indeed considerable, says Heffelfinger. "We can learn a tremendous amount by a comparative knowledge of the diversity of microbes."

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