nature REVIEWS
MICROBIOLOGY

Metagenomics: window to the microbial universe

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Metagenomics — the genomic analysis of communities of organisms — is reshaping the landscape of microbiology. Transcending individual genes and genomes, metagenomics offers access to all of the genomes in a community to reveal the secrets of the 'uncultured world' — the enormous number of microbial species that cannot currently be isolated into pure culture. Metagenomics will expand our ability to discover and benefit from microbial capabilities, improve our understanding of microbial communities and probably lead to major advances in medicine, agriculture, energy production and bioremediation.

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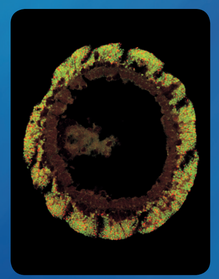
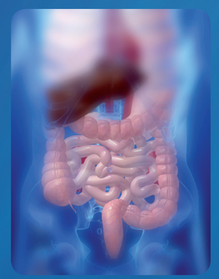
The process

Metagenomics involves isolating DNA from environmental sources and cloning it into vectors that replicate in cultured organisms. This schematic illustrates a typical metagenomics process.

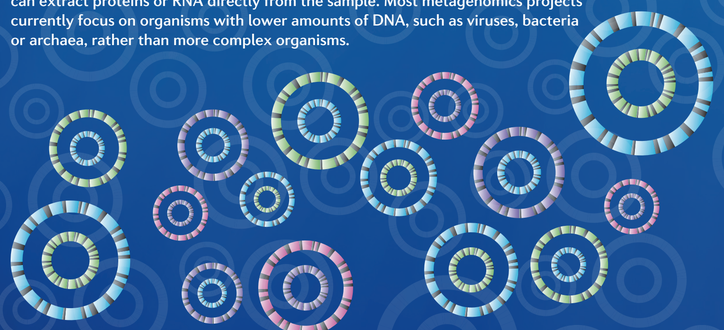
1. Sampling

Samples can be taken from any environment, including invertebrates, the human gut and deep-sea vents.

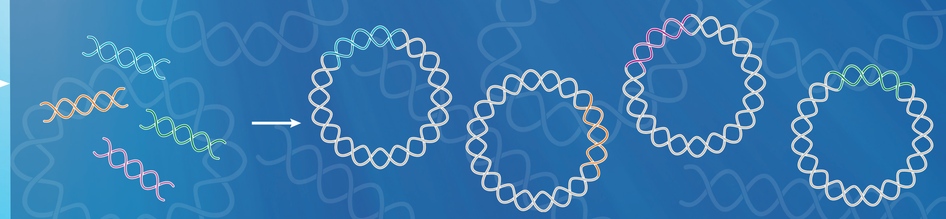

2. Extraction of DNA

Genomic DNA is extracted directly from the sample to yield DNA fragments from all members of the microbial community. DNA is then analysed directly or is cloned prior to analysis. New methods can extract proteins or RNA directly from the sample. Most metagenomics projects currently focus on organisms with lower amounts of DNA, such as viruses, bacteria or archaea, rather than more complex organisms.



3. Construction of a metagenomic library

Community DNA is fragmented and cloned into plasmids for study and preservation. Plasmids are introduced into bacteria to create a metagenomic library — a living repository of all the DNA from the sampled microbial community.



4. Analysis

a. *Sequence-based metagenomics*: provides information on the distribution of functions in a community, linkage of traits, genomic organization and horizontal gene transfer.

Approaches typically involve either sequencing of random clones to accumulate vast stores of sequence information or identification of clones based on methods that detect a particular sequence. With both of these approaches, phylogenetic markers are sought on the clone of interest to link cloned sequences with the probable origin of the DNA.

b. *Function-based analysis*: enables identification of new enzymes, antibiotics or other reagents in libraries from diverse environments.

Approaches include:

Heterologous expression, in which clones that express the desired function are identified. An important limitation to heterologous expression is that the domesticated host bacterium must be able to express (transcribe and translate) the genes for the products to be detected.

Selections, in which the clone expressing the desired function grows and others do not. Selections provide the most powerful approach to finding rare clones. Selectable characteristics include antibiotic resistance and metal resistance.
A 'functional-anchor approach' involves identifying all of the clones that express a certain function and sequencing them completely to determine the diversity of genomic environments from which that function originates.

Illuminating biology

Metagenomics could answer some fundamental biological questions. Microbial communities are composed of thousands or millions of different but interdependent individuals; some are closely related enough to be considered the same species, whereas others have few genes in common. Genetic material in these communities is often passed from one individual to another, which poses questions such as: what is a genome; what is a species; how diverse is life; how do microbial communities react to change; and how do microorganisms evolve?

Metagenomics is uniquely suited for identifying genes involved in competition or cooperation. Such genes are almost impossible to identify outside of the community context, but metagenomic analysis can yield informative insights. Investigations of communication among bacteria, for example, have found that subinhibitory concentrations of many antibiotics induce quorum sensing. Using metagenomics to screen for signalling and inhibitory compounds might therefore yield molecules that are quorum-sensing inducers as well as antibiotics. Metagenomics can also support community-wide assessments of metabolic and geochemical functions.

Cross-disciplinary applications

Metagenomics makes possible insights that could help to address some of the most complex medical, environmental, agricultural and economic challenges in today's world.

Medicine: understanding how the microbial communities that inhabit our bodies affect human health could lead to new strategies for diagnosing, treating and preventing diseases.

Earth sciences: exploring how microbial communities in the soil and ocean affect the atmosphere and environmental conditions could help us understand, predict and address global changes.

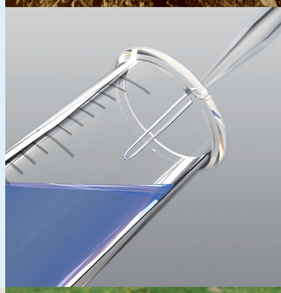
Alternative energy: harnessing the power of microbial communities might result in sustainable and eco-friendly bioenergy sources.

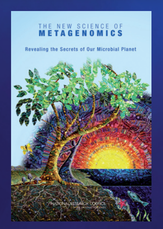
Environmental remediation: metagenomics could aid the development of microorganism-based tools for monitoring environmental damage and cleaning up oil spills, groundwater, sewage, nuclear waste and other hazards.

Biotechnology: taking advantage of the functions of microbial communities might lead to the development of new functional food and health products.

Agriculture: understanding the roles of beneficial microorganisms living in, on and around domesticated plants and animals could enable detection of diseases in crops and livestock, and aid the development of improved farming practices.

Biodefence and microbial forensics: studying the DNA and biochemical fingerprints of microbial communities helps to monitor pathogens, create more effective vaccines and therapeutics against bioterror agents, and reconstruct attacks that involve microorganisms.

Acknowledgements
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http://www.nature.com/nrmicro/posters/metagenomics

In section 1 (sampling), the image on the left shows a fluorescence *in situ* hybridization micrograph that revealed the symbiotic bacteria (red and green) that are present under the skin of the marine gutless worm *Olavius algarvensis*, which lives in the shallow-water sands off the coast of the Mediterranean. The image was kindly supplied by N. Dubilier, Max Planck Institute for Marine Microbiology, Bremen, Germany. The image on the right shows a tube-worm bush that is located near vent Marker 33. The image was taken at the NeMO seafloor observatory during an expedition that was funded by the National Oceanic and Atmospheric Administration (NOAA) Vents Program. The image was kindly provided by J. Huber, Josephine Bay Paul Center, Massachusetts, USA.

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