

Metagenomics

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Metagenomics is the study of **metagenomes**, genetic material recovered directly from environmental samples. The broad field may also be referred to as **environmental genomics**, **ecogenomics** or **community genomics**. Traditional microbiology and microbial genome sequencing rely upon cultivated clonal cultures. This relatively new field of genetic research enables studies of organisms that are not easily cultured in a laboratory as well as studies of organisms in their natural environment.^{[1][2]}

Early environmental gene sequencing cloned specific genes (often the 16S rRNA gene) to produce a profile of diversity in a natural sample. Such work revealed that the vast majority of microbial biodiversity had been missed by cultivation-based methods.^[3] Recent studies use "shotgun" Sanger sequencing or massively parallel pyrosequencing to get (mostly) unbiased samples of all genes from all members of sampled communities.^[4]

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History

Origin of the term

The term "metagenomics" was first used by Jo Handelsman, Jon Clardy, Robert M. Goodman, and others, and first appeared in publication in 1998.^[5] The term metagenome referenced the idea that a collection of genes sequenced from the environment could be analyzed in a way analogous to the study of a single genome. The exploding interest in environmental genetics, along with the buzzword-like nature of the term, has resulted in the broader use of metagenomics to describe any sequencing of genetic material from environmental (i.e. uncultured) samples, even work that focuses on one organism or gene. Recently, Kevin Chen and Lior Pachter (researchers at the University of California, Berkeley) defined metagenomics as "the application of modern genomics techniques to the study of communities of microbial organisms directly in their natural environments, bypassing the need for isolation and lab cultivation of individual species."^[6]

Environmental gene surveys

Conventional sequencing begins with a culture of identical cells as a source of DNA. However, early metagenomic studies revealed that there are probably large groups of microorganisms in many environments that cannot be cultured and thus cannot be sequenced. These early studies focused on 16S ribosomal RNA sequences which are relatively short, often conserved within a species, and generally different between species. Many 16S rRNA sequences have been found which do not belong to any known cultured species, indicating that there are numerous non-isolated organisms out there.

Early molecular work in the field was conducted by Norman R. Pace and colleagues, who used PCR to explore the diversity of ribosomal RNA sequences.^[7] The insights gained from these breakthrough studies led Pace to propose the idea of cloning DNA directly from environmental samples as early as 1985.^[8] This led to the first report of isolating and cloning bulk DNA from an environmental sample, published by Pace and colleagues in 1991^[9] while Pace was in the Department of Biology at Indiana University. Considerable efforts ensured that these were not PCR false positives and supported the existence of a complex community of unexplored species. Although this methodology was limited to exploring highly conserved, non-protein coding genes, it did support early microbial morphology-based observations that diversity was far more complex than was known by culturing methods.

Soon after that, Healy reported the metagenomic isolation of functional genes from "zoolibraries" constructed from a complex culture of environmental organisms grown in the laboratory on dried grasses in 1995.^[10] After leaving the Pace laboratory, Ed DeLong continued in the field and has published work that has largely laid the groundwork for environmental phylogenies based on signature 16S sequences, beginning with his group's construction of libraries from marine samples.^[11]

Longer sequences from environmental samples

Recovery of DNA sequences longer than a few thousand base pairs from environmental samples was very difficult until recent advances in molecular biological techniques, particularly related to constructing libraries in bacterial artificial chromosomes (BACs), provided better vectors for molecular cloning.^[12]

Shotgun metagenomics

Advances in bioinformatics, refinements of DNA amplification, and proliferation of computational power have greatly aided the analysis of DNA sequences recovered from environmental samples. These advances have enabled the adaptation of shotgun sequencing to metagenomic samples. The approach, used to sequence many cultured microorganisms as well as the human genome, randomly shears DNA, sequences many short sequences, and reconstructs them into a consensus sequence.

In 2002, Mya Breitbart, Forest Rohwer, and colleagues used environmental shotgun sequencing to show that 200 liters of seawater contains over 5000 different viruses.^[13] Subsequent studies showed that there are >1000 viral species in human stool and possibly a million different viruses per kilogram of marine sediment, including many bacteriophages. Essentially all of the viruses in these studies were new species. In 2004, Gene Tyson, Jill Banfield, and colleagues at the University of California, Berkeley and the Joint Genome Institute sequenced DNA extracted from an acid mine drainage system.^[14] This effort resulted in the complete, or nearly complete, genomes for a handful of bacteria and archaea that had previously resisted attempts to culture them. It was now possible to study entire genomes without the biases associated with laboratory cultures.^[15]

Global Ocean Sampling Expedition

Main article: Global Ocean Sampling Expedition

Beginning in 2003, Craig Venter, leader of the privately-funded parallel of the Human Genome Project, has led the Global Ocean Sampling Expedition, circumnavigating the globe and collecting metagenomic samples throughout. All of these samples are sequenced using shotgun sequencing, in hopes that new genomes (and therefore new organisms) would be identified. The pilot project, conducted in the Sargasso Sea, found DNA from nearly 2000 different species, including 148 types of bacteria never before seen.^[16] As of 2009, Venter has circumnavigated the globe and thoroughly explored the West Coast of the United States, and is currently in the midst of a two-year expedition to explore the Baltic, Mediterranean and Black Seas.

Pyrosequencing

In 2006 Robert Edwards, Forest Rohwer, and colleagues at San Diego State University published the first sequences of environmental samples generated with so-called next generation sequencing, in this case chip-based pyrosequencing developed by 454 Life Sciences.^[17] This technique for sequencing DNA generates shorter fragments than conventional techniques, however this limitation is compensated for by the very large number of sequences generated. In addition, this technique does not require cloning the DNA before sequencing, removing one of the main biases in metagenomics.

MEGAN

In 2007, Daniel Huson and Stephan Schuster developed and published the first stand-alone metagenome analysis tool, MEGAN, which can be used to perform a first analysis of a metagenomic shotgun dataset. This tool was originally developed to analyse the metagenome of a mammoth sample.^[18] However in a recent study by Monzoorul et al. 2009,^[19] it was shown that adopting the LCA approach (of MEGAN) solely based on bit-score of the alignment leads to a number of false positive assignments especially in the context of metagenomic sequences originating from new organisms. This study proposed a new approach called SORT-ITEMS which used several alignment parameters to increase the accuracy of assignments.

MG-RAST

In 2007, Folker Meyer and Robert Edwards and a team at Argonne National Laboratory and the University of Chicago released the Metagenomics RAST server (<http://metagenomics.anl.gov>) (MG-RAST) a community resource for metagenome data set analysis.^[20] The SEED (<http://www.theseed.org/>) based free, public resource has so far (October 2009) been used for the analysis of over 4000 metagenome data sets. As of October 2009 100+ giga-basepairs of DNA have been analyzed via MG-RAST, more than 350 public data sets are freely available for comparison within MG-RAST.

Applications

Metagenomics can improve strategies for monitoring the impact of pollutants on ecosystems and for cleaning up contaminated environments. Increased understanding of how microbial communities cope with pollutants is helping assess the potential of contaminated sites to recover from pollution and increase the chances of bioaugmentation or biostimulation trials to succeed.^[21]

Recent progress in mining the rich genetic resource of non-culturable microbes has led to the discovery of new genes, enzymes, and natural products. The impact of metagenomics is witnessed in the development of commodity and fine chemicals, agrochemicals and pharmaceuticals where the benefit of enzyme-catalyzed chiral synthesis is increasingly recognized.^[22]

Metagenomic sequencing is being used to characterize the microbial communities from 15-18 body sites from at least 250 individuals. This is part of the Human Microbiome initiative with primary goals to determine if there is a core human microbiome, to understand the changes in the human microbiome that can be correlated with human health, and to develop new technological and bioinformatics tools to support these goals.^[23]

It is well known that the vast majority of microbes have not been cultivated. Functional metagenomics strategies are being used to explore the interactions between plants and microbes through cultivation-independent study of the microbial communities.^[24]

Microbial diversity

Much of the interest in metagenomics comes from the discovery that the vast majority of microorganisms had previously gone unnoticed. Traditional microbiological methods relied upon laboratory cultures of organisms. Surveys of ribosomal RNA (rRNA) genes taken directly from the environment revealed that cultivation based methods find less than 1% of the bacteria and archaea species in a sample.^[3]

Gene surveys

Shotgun sequencing and screens of clone libraries reveal genes present in environmental samples. This provides information both on which organisms are present and what metabolic processes are possible in the community. This can be helpful in understanding the ecology of a community, particularly if multiple samples are compared to each other.^[25]

Environmental genomes

Shotgun metagenomics also is capable of sequencing nearly complete microbial genomes directly from the environment.^[14] Because the collection of DNA from an environment is largely uncontrolled, the most abundant organisms in an environmental sample are most highly represented in the resulting sequence data. To achieve the high coverage needed to fully resolve the genomes of underrepresented community members, large samples, often prohibitively so, are needed. On the other hand, the random nature of shotgun sequencing ensures that many of these organisms will be represented by at least some small sequence segments. Due to the limitations of microbial isolation methods, the vast majority of these organisms would go unnoticed using traditional culturing techniques.

Community metabolism

Many bacterial communities show significant division of labor in metabolism. Waste products of some organisms are metabolites for others. Working together they turn raw resources into fully metabolized waste. Using comparative gene studies and expression experiments with microarrays or proteomics researchers can piece together a metabolic network that goes beyond species boundaries. Such studies require detailed knowledge about which versions of which proteins are coded by which species and even by which strains of which species. Therefore, community genomic information is another fundamental tool (with metabolomics and proteomics) in the quest to determine how metabolites are transferred and transformed by a community.

See also

- Pathogenomics

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- Metagenomics and Our Microbial Planet (<http://dels.nas.edu/metagenomics/>) A website on metagenomics and the vital role of microbes on Earth from the National Academies. (<http://nationalacademies.org>)
- The New Science of Metagenomics: Revealing the Secrets of Our Microbial Planet (http://books.nap.edu/catalog.php?record_id=11902) A report released by the National Research Council in March 2007. Also, see the Report In Brief. (http://dels.nas.edu/dels/rpt_briefs/metagenomics_brief_final.pdf)
- IMG/M (<http://img.jgi.doe.gov/m>) The Integrated Microbial Genomes system, for metagenome analysis by the DOE-JGI.
- CAMERA (<http://camera.calit2.net/index.php>) Cyberinfrastructure for Metagenomics, data repository and tools for metagenomics research.
- A good overview of metagenomics from the Science Creative Quarterly (<http://www.scq.ubc.ca/?p=509>)
- list of Metagenome Projects from genomesonline.org (<http://www.genomesonline.org/gold.cgi?want=Metagenomes>)
- MG-RAST (<http://metagenomics.nmpdr.org>) publicly available, free, metagenomics annotation pipeline and repository for pyrosequences, Sanger sequences, and other sequence approaches.
- METAREP (<http://www.jcvi.org/metarep>) : JCVI Metagenomics Reports - an open source (<http://github.com/jcvi/METAREP>) tool for high-performance comparative metagenomics
- Human microbiome project
- MetaHIT (<http://www.metahit.eu/>) official website for the EU-funded project : Metagenomics of the

Human Intestinal Tract

- Annotathon (<http://annotathon.univ-mrs.fr/>) Bioinformatics Training Through Metagenomic Sequence Annotation
- Metagenomics (<http://www.highveld.com/pages/metagenomics.html>) Metagenomics research and applications.
- Metagenomics: Sequences from the Environment (<http://www.ncbi.nlm.nih.gov/books/NBK6858>) free ebook from NCBI Bookshelf.

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