

# Applied Sequencing Center Initiative

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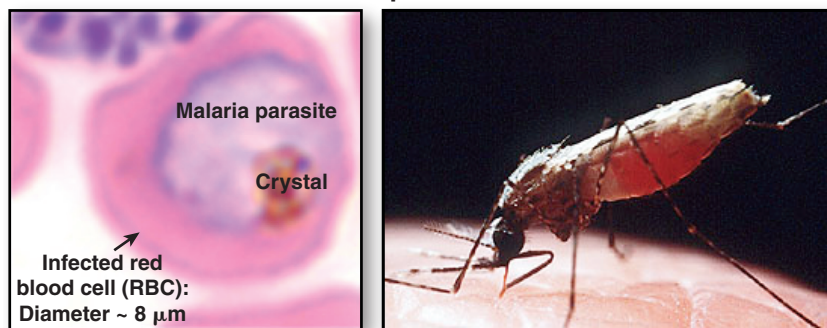
ethods for rapid, high-throughput sequencing of nucleic acids (DNA) are evolving at a breakneck pace to meet the future needs in the field of individualized genetic medicine.<sup>1,2</sup>

A major goal is the sequencing of an individual's entire genome (3 billion base pairs) in just a few hours and at a reasonable cost (~\$1000). APL has initiated several breakthrough projects, funded by current APL Independent Research and Development (IR&D) and external sponsors, that demonstrate the potential of such next-generation sequencing technologies to meet current and future APL sponsor needs in diverse fields. These proof-of-principle projects include tactical biometric tracking of individuals by using mitochondrial DNA recovered from deposited fingerprint residues, detection of novel

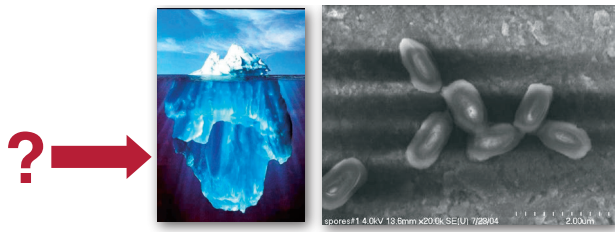
and emerging microorganisms in complex environmental samples, and biological forensics using mitochondrial DNA sequences to determine a person's geographic ancestry and to genetically "fingerprint" the host cell cultures for viral biological agents (Figs. 1 and 2). These projects have served as a platform for technical reconnaissance, and they have elucidated the longer-term potential of the emerging sequencing technologies to address a wide, cross-cutting spectrum of applications.

These applications not only address current and future APL sponsor needs but also synergistically address the JHU enterprise missions in developing new technologies for public health and medicine. Synergistic applications include molecular epidemiology for tracking and forensically sourcing disease outbreaks; affordable large-scale monitoring of emerging diseases of human, animal, or plant origin; and affordable population diversity analysis to track and monitor population traits, such as antimicrobial drug resistance (e.g., tuberculosis bacteria and malaria parasites) by using pooled sampling methods. There are also space applications, where microbial populations

## Microbial Population Genetics



**Figure 1.** Deep DNA sequencing can reveal low copy number genetic variations, enabling microbial population genetics studies (such as discerning mixed populations of malaria parasites in a single drop of blood) or person identification from small amounts of sample.



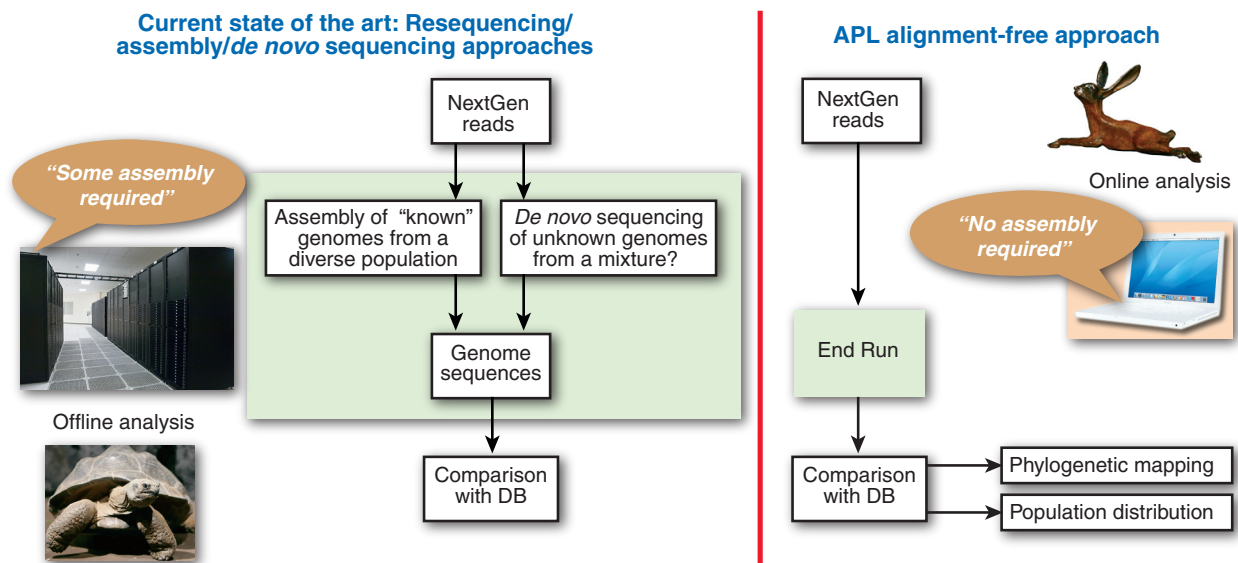
**Figure 2.** Current methods for identification of microorganisms, such as *Bacillus* spores (micrograph on the right), address only a very small portion of the microbial genome (the tip of the iceberg). Next-generation DNA sequencing methods allow us to examine the complete genome (the entire iceberg) for both identification and microbial forensics purposes.

in cleanrooms need to be characterized to monitor for potential, inadvertent colonization of planets by planetary probes.

The application of next-generation sequencing to the above scientific challenges is in process via a new sequencing center initiative. Our early forays into sequencing have enabled us to understand the major technical roadblocks and to formulate a comprehensive R&D strategy on several of these fronts. Successful

development and transition of the applications will critically depend on the development of novel, “out-of-the-box” approaches for front-end sample processing before sequencing and novel bioinformatics tools for analysis of the massive sequence data generated from complex mixtures of DNA (Fig. 3).

An important key to success is APL’s ability to directly leverage already existing JHU resources and expertise. The central goal of this APL initiative thus is to establish a center of basic and applied research activity within the JHU enterprise that addresses the major critical application roadblocks. The center seeks to facilitate coordination of related efforts across the JHU enterprise and achieve mutual long-term, synergistic research goals with high leverage for all program participants. This center should place APL at the forefront of this technology and will strengthen our ties with the rest of the University for the longer term in this critical aspect of “new biology.” These ties, and their transparency to APL sponsors through establishment of this center, will provide APL with a unique asset through which we can engage multiple sponsors across multiple application domains and attract JHU faculty, through mutual benefit, to help address problems of interest to APL sponsors.



**Figure 3.** Comparison of the current state-of-the-art sequencing method using resequencing, assembly, and *de novo* sequencing approaches<sup>3</sup> and the APL alignment-free approach.

For further information on the work reported here, see the references below or contact [andrew.feldman@jhuapl.edu](mailto:andrew.feldman@jhuapl.edu).

<sup>1</sup>Schuster, S. C., “Next-Generation Sequencing Transforms Today’s Biology,” *Nat. Methods* 5(1), 16–18 (2008).

<sup>2</sup>Mardis, E. R., “The Impact of Next-Generation Sequencing Technology on Genetics,” *Trends Genet.* 24(3), 133–141 (2008).

<sup>3</sup>Pop, M., and Salzberg, S. L., “Bioinformatics Challenges of New Sequencing Technology,” *Trends Genet.* 24(3), 142–149 (2008).