Nanopores promise cost savings in gene sequencing

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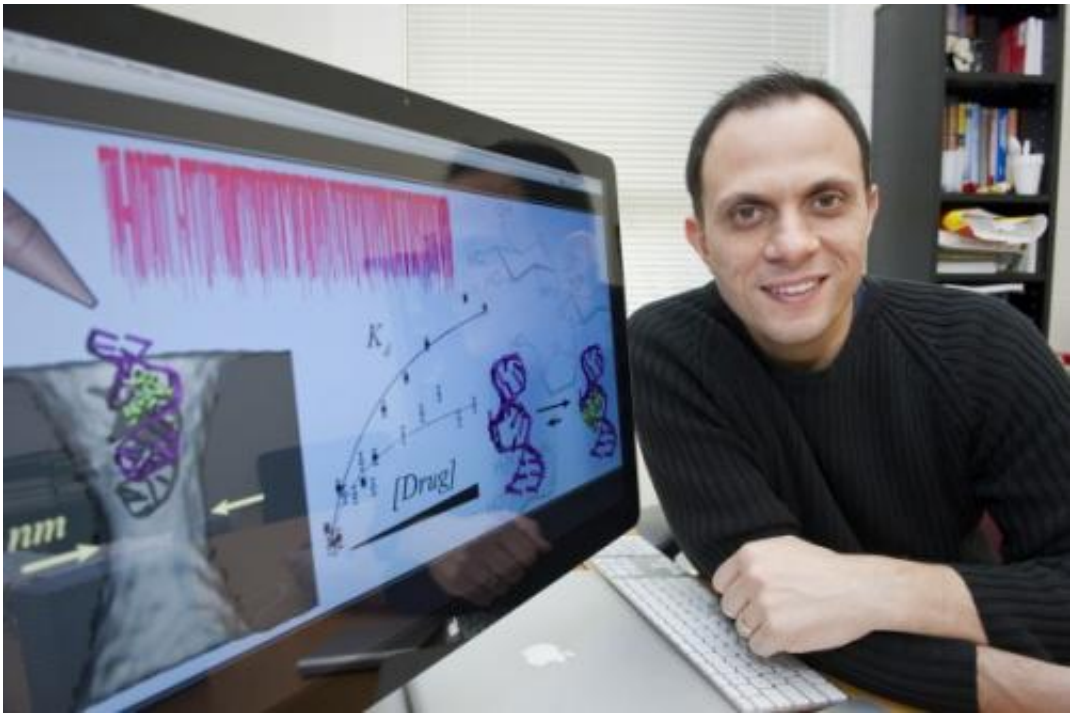

Assistant professor of physics Meni Wanunu uses nanopores to read a gene sequence one strand of DNA at a time.

(Phys.org)—In the last five years, next-generation gene sequencing has brought down the cost of unlocking a single genome from $10 million to $10,000. While the savings is unprecedented, more can still be done to reduce the cost even further, an effort that would enable a host of applications in medical research and healthcare.

Meni Wanunu, an assistant professor of physics at Northeastern University, says his work in nanopore sequencing represents one such effort. Traditionally, Wanunu has used nanopores as a DNA readout device, wherein a single strand of DNA passes through the pore causing minute changes to the surrounding electrical signal that reports on its structure.

But now he's doing the opposite: "We'll use the nanopore to hold a molecule fixed in space," Wanunu explains.

Backed by a recent $825,000 grant from the National Institutes of Health, Wanunu will apply nanopores to another sequencing technology that reads exactly one strand of DNA at a time.

Pacific Biosciences, Wanunu's grant partner, has designed a sequencing device called a SMRT Cell for single-molecule, real-time analysis. SMRT cells have the potential to bring gene-sequencing costs down to $100 per genome, but they must first overcome some significant hurdles.

Each aluminum SMRT cell contains 150,000 holes. Each hole is 100 nanometers wide and should contain one "polymerase," a molecule whose native responsibility in a living cell is to replicate a DNA sequence, one nucleotide base at a time. Polymerases are nature's best DNA sequencers and SMRT cells take advantage of a molecule with millions of years of evolution behind it.

But according to Wanunu, only about 37 percent of the holes in a SMRT cell can theoretically contain exactly one polymerase, because there's no technology to put exactly one polymerase in each hole. While 100 nanometers may seem small, one of Wanunu's nanopores is 100 times smaller.

The goal of the research backed by the new grant is to match each SMRT cell hole with a single nanopore. Sitting above the nanopore, each

polymerase will be attached to an anchor below it, thus preventing the former from floating away.

By ensuring that there is a single polymerase in each hole, the nanopore approach will increase the number of gene sequences that can be read at once, improving the overall yield of the SMRT cell. Additionally, since nanopores are so small, it's possible to create a voltage gradient across them, driving charged DNA strands toward the holes, and thus increasing the sensitivity of the sequencer to DNA molecules.

"The niche here is sequencing native DNA that cannot be amplified," Wanunu says. Epigenetic markers, for example, which sit on top of our genes and regulate expression, are lost when DNA is amplified—a standard process in most sequencing technologies. By reading DNA one strand at a time, then, the SMRT cell would not only decrease costs but would also enable a new frontier in genome research.

Provided by Northeastern University