Study questions feasibility of entire genome sequencing in minutes

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The claim that nanopore technology is on the verge of making DNA analysis so fast and cheap that a person's entire genome could be sequenced in just minutes and at a fraction of the cost of available commercial methods, has resulted in overwhelming academic, industrial, and global interest. But a review by Northeastern University physicist Meni Wanunu, published in a special issue on nanopore sequencing in *Physics of Life Reviews*, questions whether the remaining technical hurdles can be overcome to create a workable, easily produced commercial device.

Earlier this year Oxford Nanopore Technologies, one of the pioneering companies of sequencing discoveries, announced that they expect nanopore strand sequencing to achieve a 15-minute genome by 2014 at a cost of $1,500. This is a far cry from the $10 million it cost to sequence an entire genome just 5 years ago.

Since the idea of nanopore sequencing was first proposed in the mid 1990s, huge advances have been made. The basic idea is exceedingly simple: a single thread of DNA is passed through a tiny molecule-sized hole—or nanopore—and the various DNA bases are identified in sequence as they move through the pore.

But according to Wanunu, the reality of manipulating technology based on pores so tiny that 25,000 of them can fit side by side on a human hair has proved a daunting task. The main challenge has been to slow the process down and control the movement of the DNA strand through the

pore at a rate slow enough to make individual DNA bases readable and usable. A new approach using enzyme-controlled movement, developed to overcome this problem, has its own drawbacks including poor enzyme activity resulting in limited processivity and uncontrolled forward-reverse motion.

Another major dilemma has been whether protein or solid-state pores provide the most promising technique. At first, naturally occurring porous proteins were investigated. But in the early 2000s, heralded as offering better capability and flexibility, various solid-state nanopores made of silicon or graphene were tested. "Since both lipid-embedded protein channels and solid-state nanopores have drawbacks, it will be interesting to see which device, or what combination of devices, will be available in years to come, if any," Wanunu says.

At this time there are still many hurdles to overcome, he adds, including the inability of nanopores to provide any spectroscopic information about the identity of a molecule, uncertainties about whether translocation occurs at a constant speed, and the complications of pore clogging.

Writing in a comment published in the same issue, John Kasianowicz from the National Institute of Standards and Technology in the US, a pioneer in the field, agrees that plenty of challenges remain: "There are indeed still many problems to address in order to enable practical electronic nanopore-based sensing devices. However, by better understanding the road already developed in this nascent field, the journey will hopefully appear a little less daunting,"

In a final comment on Wanunu's review, the founder and Director of Oxford Nanopore, Hagan Bayley, looks ahead to the future: "In the longer term, by using solid-state pores… it may be possible to read DNA sequences at microseconds rather than milliseconds per base. This could

be done by using tunnelling currents or other characteristics of the DNA bases for which graphene—with its unusual electronic properties—might after additional development provide a superior substrate and in so doing deliver another massive leap forward on top of a decade of unprecedented progress."

More information: "Nanopores: A journey towards DNA sequencing" by Meni Wanunu (dx.doi.org/10.1016/j.plrev.2012.05.010) The commentaries on the review are: Bio-inspired nanopore-based sensors by John J. Kasianowicz.

(dx.doi.org/10.1016/j.plrev.2012.05.012); Are we there yet? By Hagan Bayley.
(dx.doi.org/10.1016/j.plrev.2012.05.015). The study and commentaries appear in Physics of Life Reviews Vol 9, Issue 2 (June 2012).

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