Next-generation genome sequencers compared

Three main platforms compete in head-to-head battle.

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Desktop sequencers promise to democratize genomics, but it is difficult for researchers who are not experts in sequencing technology to sort through the overheated marketing claims made in this fiercely competitive industry. A group of UK-based researchers therefore decided to put the three leading models — Roche's 454 GS Junior, Illumina's MiSeq and Life Technologies' Ion Torrent Personal Genome Machine (PGM) — through their paces. The test was to sequence the genome of the bacterium *Escherichia coli*, which killed more than 40 people in Germany last summer.

Nature spoke to Nicholas Loman, a bioinformatician at the University of Birmingham, UK, and one of the authors of the study, asking him what the work reveals about the state of genetic microbial diagnostics. The results are published today in *Nature Biotechnology*[1].

Roche Diagnostics/Illumina/Life Technologies

An analysis of three leading sequencers has shown that there is no one-size-fits-all solution for biologists.

So who won?

Each platform has strengths and weaknesses. If you want the most throughout per hour, the Ion Torrent PGM does that. If you need the highest throughput per run, the MiSeq is there. Accuracy-wise, the MiSeq is best; for generating the longest reads, the 454 is best. Both the PGM and 454 have some problems with accuracy concerning homopolymers [stretches of repeating bases]. And, of course, a user is going to want to look at cost. Part of the point of our paper is that genome sequencing is not a one-size-fits-all solution.

Why did you do this analysis?

As next-generation genome sequencing is going to come into the clinic and into public health, it will be targeted at people who don't necessarily fully understand these issues. Up until now, people have had to depend on marketing information and blog posts for these comparisons, which are really useful, but can be difficult to find. And the marketing is really quite aggressive, if you remember the Personal Genome Machine vs MiSeq videos that played off the Mac vs PC ads. People are crying out for independent analysis.

Can you put the error rates you saw into context?

We tried to combine the two major sources of errors, which are nucleotide substitutions [when the sequencer reads an incorrect base] and indels due to homopolymers [insertions and deletions of incorrect sequence data]. We found that these indel errors happened with the PGM and the 454 machines even in short homopolymeric tracts. The issue here is the homopolymeric-tract error is a systematic error, which means that even if you load and run the samples lots and lots of times, the error remains. If you're trying to detangle sequencer error from a result that is biologically plausible, that's going to be very difficult to do, and it's going to inhibit your ability to do good public-health analysis of bacterial genomes.

What do your results say about desktop sequencing for analysing, say, previously unknown pathogen strains in public-health clinics?

All of these systems require some manual curation of the data. But it's not realistic to have an army of bioinformaticians or evolutionary genomicists sitting down and doing this in every regional public-health lab. People might say, "I can get a genome sequencer and they all do whole genomes, so it doesn't matter which one I get", but they need to think carefully about how they're going to deploy these machines.

Would your analysis be any different if you did it again, considering that these platforms are still evolving?

There are always going to be fundamental issues related to the sequencing chemistries, and all of the instruments use some variant of PCR [polymerase chain reaction, which amplifies the original samples], so issues related to that are not issues that can be got rid of. I think our findings about the relative performance of the instruments are likely to be relatively sound moving forward.

Do you hope that your paper will inspire other comparisons of sequencing machines?

These kinds of comparisons are fairly rare, and there's definitely more scope for systematic evaluation of platforms. At the moment a lot of the comparison is done by rumour and innuendo, and there's definitely scope for opening that up. And nowadays, a lot of these platforms let you put your results straight into the cloud, so there's no reason why that can't happen.

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References

1. Loman, N. J. *et al*. *Nature Biotechnol.* http://dx.doi.org/10.1038/nbt.2198 (2012).