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EXBs - exponentially-expanded barcodes for highly accurate single molecule profiling

Researchers at Stanford have developed a high-throughput barcoding method that greatly improves sequencing accuracy and makes it possible to do robust single molecule profiling, since it can trace duplicate sequencing reads to their original single molecule clones. Characterization of genetic information in biological samples requires both accurate quantification and characterization of variants. Recently, molecular barcodes have been developed to improve gene expression measures, especially for low input amounts and for single cell transcriptome analysis. However, current barcoding methods either do not scale up well or are prone to sequencing errors that disrupt analysis. To overcome these limitations, the inventors have developed exponentially-expanded barcodes (EXBs). EXBs use a computationally designed set of highly error-resistant barcodes followed by a combinatorial enzymatic assembly process to generate high diversity without sacrificing robustness. This method generates exponentially large numbers of unique, rationally-designed barcodes that can be used to accurately quantify each molecular species present in the sequencing reaction.

Stage of Research

To assess the method's performance, the researchers have applied it to known gene expression standards at varying input amounts, and to the analysis of single cells. They found EXBs are superior to other barcoding methods, since they enable molecular tagging that is resistant to errors for both bulk and single cell transcriptomes.

Co-inventor Billy Lau gives an overview of the technology.

Applications

- Analysis of sequencing results:
  - Single molecule profiling and rare mutation confirmation
  - Quantification of molecular species
  - Distinguishing between PCR duplicates and distinct molecules in amplicon or deep resequencing
  - Confirmation of mutations at low sequencing depth

Advantages

- Highly scalable (~10"10 and higher)
- Easily modified to larger and smaller barcodes sizes
- Robust and systematic generation of barcodes
- Robust mapping to designed barcode
- Resistant to PCR and sequencing errors
- Applicable to bulk and single cell transcriptomes

Publications

- Billy T. Lau and Hanlee P. Ji, "Single molecule counting and assessment of random molecular tagging errors with transposable giga-scale error-correcting barcodes," BMC Genomics, September 21, 2017, https://doi.org/10.1186/s12864-017-4141-4.
- PCT Application, “Robust Quantification of Single Molecules in Next-Generation Sequencing Using Non-Random Combinatorial Oligonucleotide Barcodes,” published 10/20/2016 (Publication No. 2016168351).

Patents

- Published Application: WO2016168351
- Published Application: 20180100145
- Issued: 11,661,597 (USA)

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