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# Modeling a High-Throughput Barcode Molecule Reader for Single-Molecule Omics

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Emerging nanopore technologies promise substantial advancements in large-scale molecular analysis or omics. One of the profound challenges lies in the staggering concentration disparities inherent in proteomes. For instance, within a single cell, this dynamic range can span up to seven orders of magnitude, while in blood plasma, it can exceed a mind-boggling  $10^{12}$ -fold. To surpass the limited dynamic range typically achievable with mass spectrometry (ranging from  $10^3$  to  $10^5$ ), nanopore-based single-molecule techniques must analyze billions of individual molecules. To process a sample with a dynamic range of  $10^{12}$  within an hour, the required read throughput must reach the scale of billions of molecules per minute. Such throughput remains beyond the grasp of current technological capabilities.

Impressive progress has been accomplished in discriminating single amino acids with nanopores. However, requiring such resolution directly from the reader may not be conducive to achieving the highest possible single-molecule throughput.

To significantly enhance throughput levels, our proposed approach leverages DNA structural barcodes, comprising a DNA strand as a backbone adorned with multiple labels for information encoding [1,2]. These barcode molecules act as intermediaries. We envision a transformation of the proteome into these barcodes, which are subsequently isolated within a purified mixture, and read-out by a high-bandwidth solid-state nanopore array integrated with silicon electronics. Several proteomics assays, such as Somalogic, Olink, and Encodia assays, are already established or in development and adept at translating the proteome to DNA. Despite the larger bit length of structural DNA barcodes, they offer a considerably higher information throughput compared to nanopore sequencing. This advantage stems from the rapid read-out at high translocation speeds, facilitated by less sensitive but significantly higher bandwidth solid-state pores. By decoupling protein recognition or sequencing from the reader, we can harness both the paramount, three-dimensional parallelism of biochemistry, and the speed of nanoelectronics.

We will delve into comprehensive modeling to substantiate the superior performance of our high-throughput barcode reader concept, encompassing aspects from barcode preconditioning and capture, to the high-speed electronics.

**References:** [1] N.A. Bell et al., Nature nanotechnology, 2016 [2] K. Chen et al., Nano letters, 2018