A124 · Genome-Scale Sub-Megabase Chromatin Tracing with DNA-MERFISH

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The 3D organization of the genome plays a critical role in gene transcription. While sub-megabase single-cell datasets collected using high-throughput chromosome conformation capture (Hi-C) have identified on the order of thousands of differential topologically-associated domain (TAD) boundaries and genomic loops at the pseudo-bulk level across cell types, these datasets are limited by a sparsity problem where incomplete single-cell contact maps often need to be filled through imputation heuristics before further analysis, preventing thorough quantification of cell-to-cell variations. On the other hand, imaging-based combinatorial chromatin tracing methods such as multiplexed error-robust fluorescence in situ hybridization (MERFISH) applied to DNA has been shown to reach up to ~80% detection efficiency in single cells at ~1 Mbp resolution, a regime too large to identify most TADs and loops. We aim to extend DNA-MERFISH towards targeting an order-of-magnitude larger number of genomic loci, thus reaching sub-megabase resolution. Using improved MERFISH single-cell chromatin traces, we aim to both identify novel cell-type-specific features relevant to biological function as well as quantify the degree of variation of domains and loops across single cells.

Genome-Scale Sub-Megabase Chromatin Tracing with DNA-MERFISH

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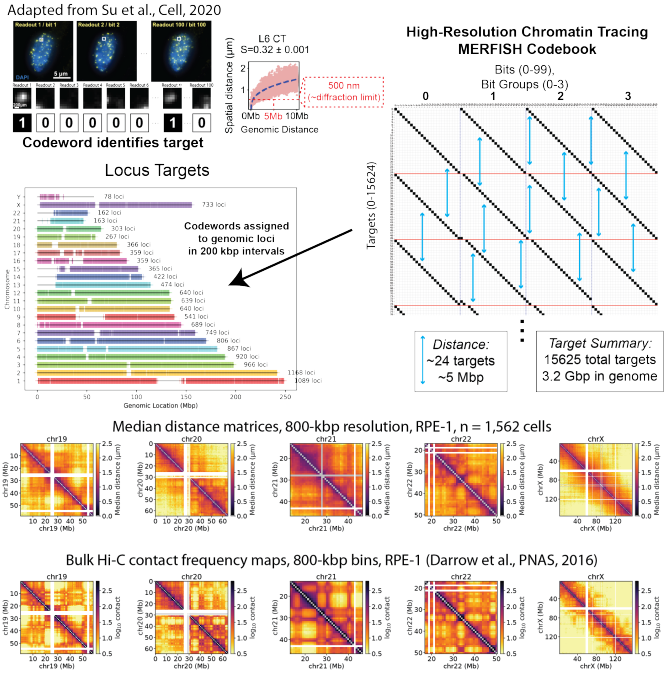
MERFISH Codebook Constraints:

(1) greater than 10,000 loci are targeted ***(sub-Mbp genome-wide resolution)***
(2) no targets likely to be within ~500 nm share a "1" bit in a given round ***(diffraction limit)***
(3) all codewords have minimum Hamming Distance 4 from all other codewords ***(error correction)***
(4) the number of bits per codewords (number of imaging rounds) is minimized ***(scalability)***



Median distance matrices, 800-kbp resolution, RPE-1, n = 1,562 cells

Bulk Hi-C contact frequency maps, 800-kbp bins, RPE-1 (Darrow et al., PNAS, 2016)