Title: Comparative analysis of spatially resolved transcriptomics data

Jean Fan, Ph.D.

Assistant Professor of Biomedical Engineering
Center for Computational Biology

Johns Hopkins University, USA

Abstract: Characterizing cells and their transcriptional states in their spatial context is important for understanding tissue function. To enable such spatially resolved transcriptomic profiling of fixed cells in tissues, recent advances in imaging technologies have enabled high-throughput in situ, targeted transcriptomic profiling of pre-selected RNAs at molecular and single-cell resolution. Similarly, technologies based on spatially resolved RNA capture followed by sequencing have enabled non-targeted, genome-wide transcriptional profiling at the multi-cellular pixel resolution. Such spatially resolved transcriptomics data demand new computational methods to take advantage of this new spatial dimension of information to derive relevant biological insights. Here, I will describe a few recent computational approaches developed in my lab for analyzing spatially resolved transcriptomics data. For analyzing single-cell resolution spatially resolved transcriptomics data, we developed MERINGUE, a computational framework based on spatial auto-correlation and cross-correlation analysis to characterize spatial gene expression heterogeneity in both 2D and 3D in a manner that is robust to the nonuniform cellular densities inherent within tissues. We apply MERINGUE to identify genes with sexually dimorphic spatially heterogeneous expression patterns within cell-types in the mouse pre-optic region. We further infer putative cell-cell communication between neuronal subtypes via paracrine signaling based on spatially cross-correlated patterns of hormone synthetase and receptor genes. For analyzing multi-cellular pixel resolution spatially resolved transcriptomics data, we developed STdeconvolve as an unsupervised approach that builds upon latent Dirichlet allocation to deconvolve underlying cell-types and recover cell-type-specific spatial organizational patterns. We show that STdeconvolve effectively recovers the putative transcriptomic profiles of cell-types and their proportional representation within spatially resolved multi-cellular pixels without reliance on external single-cell transcriptomics references. We find that STdeconvolve provides competitive performance to existing reference-based methods when suitable single-cell references are available, as well as potentially superior performance when suitable single-cell references are not available. Both MERINGUE and STdeconvolve are available on Github at https://github.com/JEFworks-Lab. Overall, we anticipate that such spatially resolved transcriptome profiling technologies coupled with spatial computational analyses could help address a wide array of questions and contribute important fundamental biological insights regarding how tissues are organized in both the healthy and diseased settings..

Biography: Dr. Jean Fan is a member of the faculty of Biomedical Engineering in the Center for Computational Biology at Johns Hopkins University. Her research team, the JEFworks lab, is interested in understanding the molecular and spatial-contextual factors shaping cellular identity and heterogeneity, particularly in the context of cancer and how this heterogeneity impacts tumor progression, therapeutic resistance, and ultimately clinical prognosis. She develops new open-source computational software for analyzing single-cell multi-omic and imaging data that can be tailored and applied to diverse cancer types and biological systems.Dr. Fan was previously an NCI F99/K00 post-doctoral fellow in the lab of Dr. Xiaowei Zhuang at Harvard University. She received her PhD in Bioinformatics and Integrative Genomics at Harvard under the mentorship of Dr. Peter Kharchenko at the Department of Biomedical Informatics and in close collaboration with Dr. Catherine Wu at the Dana-Farber Cancer Institute. The impact of Dr. Fan's work has been recognized by several awards and honors, including the Forbes 30 Under 30, the Nature Research Award for Inspiring Science, and the NSF CAREER Award.