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Lecture: Information from fluctuation: high-throughput single-molecule and single-cell imaging to probe disease mechanisms

Measuring the full distribution of molecular expression in cells is critical to understanding genetic regulatory networks. Because the molecular expression is often noisy in space, time, and between cells, it is critical to image a sufficiently large population and quantify the noise contributed by the imaging modality itself. In this lecture, I will present recent advancements in measuring large numbers of single molecules within cells and tissue, along with examples of how these rigorous experiments lead to new biological insight. First, I will introduce the biochemistry and physics that make single-molecule spectroscopy possible. Next, I will
discuss the noise sources in these experiments and how it can lead to the false positive identification of individual molecules and show how careful experimental design and data analysis can prevent this issue. I will then present our recent work on extending these measurements to intact organs and human autopsy tissue using optical tissue clearing and light-sheet microscopy. I will end with our recent study of how a mouse model with a *plp1*(a myelin compaction protein) deletion leads to subtle behavioral changes. These behavioral changes are due to unexpected and subtle spatiotemporal changes in molecular expression and cellular behavior that were only identifiable using high-throughput imaging methods.