GENETICS, BIOINFORMATICS, AND SYSTEMS BIOLOGY COLLOQUIUM

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THURSDAY MARCH 2
12:00PM PST
LIVE @ LEICHTAG & ON ZOOM!

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PASSWORD: GENOMICS

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UNTANGLING GENETIC PUZZLES WITH SPATIAL GENOME IMAGING

Over the past decade, advances in sequencing based methods have helped advance our understanding of genome organization and function from a 1D view into a new field of 3D genome organization, mapping structural organization genome wide and identifying key regulators. These advances have opened an array of new questions, not easily addressed by the available technologies but central to understanding the results. What physical 3D structures underlie the patterns in frequency-of-contact among genomic loci revealed by sequencing approaches such as Hi-C? That is to say, what does a "topologically associating domain" (TAD), a "CTCF loop", or an "architectural stripe" look like under the microscope, and how do such measurements help us understand the transcriptional regulatory potential of such features? I will describe our work developing single molecule super-resolution methods to image the 3D organization of the genome, and describe how these approaches are helping us to understand both the mechanisms which regulate genome structure and the impact of this regulation on transcriptional control in animal development. Using an imaging approach we've called Optical Reconstruction of Chromatin Architecture (ORCA), I will first show how the microscopy data, averaged across a population of cells, can map de novo these same TADs, loops and stripes, identified by deep Hi-C, helping to validate both methods, while uncovering artifacts in some related sequencing methods. I will then describe how the single-cell nature of the 3D traces uncover the highly heterogeneous, likely dynamic nature of chromatin folding, and exclude some earlier explanations of cis-regulatory specificity based on chromatin globules. Applying ORCA in spatially organized embryonic tissues, combined with multiplexed single molecule RNA analyses, we are able to follow how divergent 3D folding leads to divergent cell-fates during development and how disruption of this 3D structure can produce homeotic fate transformations. Combining ORCA with fast-acting degrons to rapidly deplete architectural proteins, I will show unpublished work on how we have mapped the key proteins CTCF and cohesin organize 3D genome folding in single cells, from the kilobase scale of single genes to the whole chromosomes. These data reveal unexpected roles for CTCF in the bypass of TAD borders and unexpected roles for cohesin in chromosome-scale 3D structure, which we find has an essential noise-damping effect of global transcription regulation. I will close with a final unpublished example of how imaging 3D chromatin structure has helped us evaluate and understand the potential roles of phase-separation and droplet formation in the function of the epigenetic repressive system of Polycomb factors.

Organization Committee: J. Gleeson, J. Sebat & BISB PhD Students
GBSBC Seminar Coordinator: W. Harabedian
BISB Seminar Coordinator: F. Perez Estrada

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