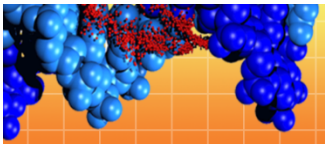

CENTER FOR BIOINFORMATICS & COMPUTATIONAL BIOLOGY

BIOINFORMATICS 2015 FALL SEMINAR SERIES

Hosted by: Department of Computer and Information Sciences,
Department of Electrical and Computer Engineering &
Center for Bioinformatics and Computational Biology
http://bioinformatics.udel.edu/Seminars/Current

MONDAY, October 5, 2015
3:30pm
DBI Room 102

Regulation of Transcription and RNA Processing in Single Cells: Understanding Heterogeneity in Gene Expression

Dan Larson

Head, Systems Biology of Gene Expression
National Cancer Institute

ABSTRACT: Gene expression refers to the sum of processes that enable cells to control their complement of RNA, and the study of gene expression has been spurred by genome-wide techniques such as microarrays and chromatin immunoprecipitation. Placing these data within a cellular context to reveal the underlying mechanisms of gene regulation has been a central challenge in the field of systems biology. In recent years, through parallel advances in microscopy, fluorescent probe development, and computational modeling, it has become possible to describe gene expression in a fundamentally different way: one can now directly observe single molecules of RNA in living and fixed cells using the fluorescence microscope. In this talk, I will describe two studies.

First, I will present our results using single-molecule imaging to study transcription kinetics of the GAL10 locus in budding yeast, which is regulated by sugar availability. Transcription is observed to occur in bursts of high activity followed by periods of inactivity, each lasting several minutes. This stochastic, punctate behavior results in 'noise' in gene expression and is not visible in population studies, which instead give the impression of a gradual response to sugar availability. I will describe recent results on the role of non-coding RNA in transcriptional regulation. Genomic data indicates that eukaryotic genomes are ubiquitously transcribed, but the function of these RNAs is largely unknown. Our results indicate that noncoding RNA displays different behavior during repression and activation, suggesting multiple roles, even at the same locus.

The second project is on stochastic RNA processing in human cells. Synthesis of mRNA in eukaryotes involves the coordinated action of many enzymatic processes, including initiation, elongation, splicing and cleavage. Kinetic competition between these processes has been proposed to determine RNA fate, yet such coupling has never been observed in vivo on single transcripts. Here, we use dual-color single-molecule RNA imaging in living human cells to construct a complete kinetic profile of transcription and splicing of the B-globin gene. We find that kinetic competition results in multiple competing pathways for pre-mRNA splicing. A single missense point mutation (S34F) in the essential splicing factor U2AF1 which occurs in human cancers perturbs this kinetic balance and defers splicing to occur entirely post-release.